

Original article

The ARGA study with Italian general practitioners: prescriptions for allergic rhinitis and adherence to ARIA guidelines

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Abstract

Background:

General practitioners (GPs) are the healthcare professionals to whom patients with rhinitis firstly refer for their symptoms.

Objective:

In the present study, we assessed drug prescriptions for allergic rhinitis (AR) and evaluated prescriptive adherence to ARIA treatment guidelines.

Methods:

Data on 1379 AR patients were collected by 107 Italian GPs. Adherence to ARIA guidelines was evaluated according to AR severity classification.

Results:

AR was diagnosed by GPs as mild intermittent for 46.2% of patients, mild persistent for 26.6%, moderate–severe intermittent for 20.2%, and moderate–severe persistent for 7%; 43.7% of AR patients had concomitant asthma. The most frequently prescribed therapeutic groups were antihistamines (anti-H, 76%) and nasal corticosteroids (NCS, 46%). Anti-H were significantly used more often to treat AR alone than AR + asthma (85 vs. 68%, $p < 0.001$), whereas NCS were used more often to treat AR + asthma than AR alone (50 vs. 42%, $p = 0.01$). Among patients with only mild intermittent AR, 39% were prescribed combined therapy. Among patients with moderate–severe persistent AR, 30% of those with AR alone and 18% of those with AR + asthma were prescribed monotherapy based on anti-H. GPs were more compliant with ARIA guidelines while treating AR alone (57%) than AR + asthma (46%) patients. The adherence increased according to the severity grade and was satisfactory for moderate–severe persistent AR (89% for AR alone and 95% for AR + asthma).

Conclusions:

Adherence to ARIA guidelines is satisfactory only for treatment of more severe patients, thus GPs often tend to treat patients independently from ARIA guidelines. Since prescription data only provide limited information to judge prescribing quality, some deviation from the gold standard are to be expected.

Introduction

Many international epidemiological studies agree that the prevalence of allergic rhinitis (AR) is still on the increase¹. AR is a global health problem affecting people from all countries, ethnic groups, socioeconomic conditions and ages, causing major illness and disability worldwide. Conservative estimates indicate

that AR occurs in over 500 million people around the world and affects social life, sleep, school and work with substantial economic impact²⁻⁴. Recently, De Marco *et al.* reported, in a sample of young adults (20–44 years), an increasing prevalence in the last two decades from 16.8 to 25.8% in Italy¹. Both AR and asthma are inflammatory conditions of the airways and often coexist. The links between these two conditions are well-characterized, and it has been proposed that AR and asthma represent a continuum of the same disease⁵. Several studies identified AR as a risk factor for asthma^{6,7}. Epidemiological investigations found an important overlap between both diseases. It was found that around 40% of AR patients had asthma, and 30–80% of asthmatic patients reported AR⁸. Italian data report about 60% of asthmatics with allergic rhinitis⁹.

The World Health Organization ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines stress the importance of these links and provide guidance for their prevention and treatment². ARIA recommendations suggest that asthma patients should be evaluated for AR, and all AR patients should undergo tests for asthma.

Patients with rhinitis and asthma consult primary care physicians, and therefore general practitioners (GPs) are encouraged to understand and use ARIA guidelines. However, many studies prove that guideline recommendations are not (or only partially) applied within clinical practice¹⁰⁻¹². Difficulties in the application of ARIA guidelines in clinical practice may be due to several factors, including poor communication within the doctor–patient relationship, structural limitations of the National Health Systems, treatment duration, or the patients' own beliefs about medications¹³, which might result in under-treatment or over-treatment of AR.

Despite the high burden of AR and asthma in the general population and the fact that GPs are among the first healthcare professionals to whom patients refer for their symptoms, there are few studies to date, concerning the allergic rhinitis management based on data directly collected in the GPs office.

The ARGA study (Italian acronym for 'Respiratory Allergies: monitoring study for the application of GINA and ARIA guidelines'), funded by Agenzia Italiana del FARMACO (AIFA, Italian acronym for 'Italian Drug Agency'), was carried out between March 2007 and February 2010. The overall aim was to monitor how the World Health Organization GINA¹⁴ and ARIA² guidelines for asthma and allergic rhinitis management are applied in clinical practice¹⁵.

This part of the study aims to: (1) assess drug prescription by GPs in patients with rhinitis alone, or rhinitis and asthma; (2) evaluate prescriptive adherence to ARIA guidelines according to rhinitis severity.

Methods

The ARGA study included several sub-projects related to different cross-sectional or longitudinal studies with specific aims. Briefly, the ARGA study was framed in four research sectors: (1) observational studies; (2) drug surveillance; (3) educational intervention; (4) prescription appropriateness and pharmacoeconomy. It involved ten units from various Italian institutions: National Institute of Health (ISS), Italian National Research Council (CNR), Medical Institutes for Hospital Admission, Care and Research (IRCCS), Universities and Local Health Services.

This study is based on the subproject of the ARGA study entitled 'Observational study on Italian General Practitioners'.

Population

Data reported in this paper look at GPs and their patients affected by allergic rhinitis. GPs were distributed throughout the three Italian macro-areas: North, Central, South-Islands. GPs' recruitment was carried out via mail among GPs who had participated in previous studies or educational courses organized by the authors.

The GPs were invited to select all patients with an AR diagnosis who had either been previously treated for AR or had presented AR-like symptoms during the past 12 months. Since in Italy children under the age of 14 years are the responsibility of family pediatricians and not of general practitioners, male and female citizens aged 14 years and over were considered eligible subjects. Subjects deemed unable to participate in the survey, and those permanently hospitalized or living in nursing homes were excluded. Participating patients provided *ex ante* their written informed consent for the purposes of the study (participation in the study, anonymous management of individual data, collective statistical analyses and anonymous publication of research results).

The study protocol, patient information sheet and consent form were approved by the ethics committee of the University Hospital of Pisa (Azienda Ospedaliero-Universitaria Pisana) on October 13, 2006 (Prot. no. 37 710 of October 25, 2006).

Data collection

GPs filled out a questionnaire to gather information on diagnosis, disease severity and prescribed drugs. GPs reported the disease diagnosis based on their clinical experience and on clinical information about the patients.

Table 1. Summary of recommendations for allergic rhinitis (AR) according to ARIA (1) guidelines.

ARIA classification	Suggested therapy
Mild intermittent	Anti-H and/or decongestants
Mild persistent	Anti-H and/or decongestants or NCS or chromones or LTRAs* or SIT
Moderate–severe intermittent	Anti-H and/or decongestants or NCS or chromones or LTRAs* or SIT
Moderate–severe persistent	NCS or Anti-H or LTRAs* and decongestant/anticholinergics/SCS or SIT

*For AR patients with concomitant asthma.

Anti-H, antihistamines; NCS, nasal corticosteroids; LTRAs, leukotriene receptor antagonists; SCS, systemic corticosteroids; SIT, specific immunotherapy.

For AR diagnosis and severity level, we considered the following questions:

- (1) ‘What kind of diagnosis have you made for your patient?’ (allergic rhinitis, asthma or both);
- (2) ‘Have you assessed the severity level of allergic rhinitis of your patients?’ (yes, no);
- (3) If yes, ‘What is the diagnosed severity level of allergic rhinitis?’ (mild intermittent, mild persistent, moderate–severe intermittent, moderate–severe persistent)².

A patient was classified as having allergic rhinitis from either a reported diagnosis or assessment of AR severity level by GPs.

As regards the AR treatment, GPs filled out a form reporting the trade name of the prescribed drugs for AR.

Statistical analyses

Statistical analyses were carried out using SPSS rel 13.0. Frequency distribution, cross tabulations, and non-parametric Mann–Whitney tests were used in order to describe the pattern of the outcomes of interest and to compare prescriptions for allergic rhinitis in relation to severity levels and AR diagnosis with or without concomitant asthma.

The therapeutic groups considered in the statistical analyses were those listed in ARIA guidelines for AR treatment.

The adherence to ARIA guidelines² was evaluated according to AR classification and considering the drugs recommended in the ARIA guidelines for the different severity levels (Table 1).

Two-tailed tests at 5% level of significance were applied in the analyses.

Results

GPs participating in the study ($n = 107$) were mostly males (79.3%). Distribution among the macro areas was: 43.1 % were in the North area, 18.6% in the Central area, and 38.2% in the South-Islands.

Table 2 reports general characteristics, diagnosis and AR severity of patients included in the present study.

Table 2. Characteristics of patients with allergic rhinitis (AR) ($N = 1379$).

Characteristic	<i>n</i> (valid %)
Gender	
Males	629 (45.6)
Females	750 (54.4)
Age, mean $\pm$ SD (median, range)	38.9 $\pm$ 15.7 (37, 14–90)
Diagnosis	
AR alone	776 (56.3)
AR + asthma	603 (43.7)
ARIA classification	
Mild intermittent	553 (46.2)
Mild persistent	318 (26.6)
Moderate–severe intermittent	242 (20.2)
Moderate–severe persistent	84 (7.0)
Not evaluated* ($n = 159$, 11.5%)	
Missing ($n = 23$, 1.7%)	

*Severity level not evaluated by GPs.

In total 1379 AR patients were enrolled, median age was 37 years (range 14–90 years), and gender was quite evenly distributed (45.6% M–54.4% F). In 11.5% of cases, GPs did not assess severity of AR, and for 1.7%, no information at all was given. Most of classified patients ($n = 817$, 73%) were diagnosed by GPs as having a mild form of the disease; of these, 46.2% were diagnosed as mild intermittent and 26.6% as mild persistent. 20.2% had moderate–severe intermittent and only 7% had moderate–severe persistent AR. In all, 43.7% of the rhinitic patients had concomitant asthma.

Allergic rhinitis treatment

Table 3 shows the distribution of therapeutic groups prescribed by GPs for AR treatment. The most frequently prescribed drugs were antihistamines (anti-H, 76%) and nasal corticosteroids (NCS, 46%). Anti-H were mostly used for patients with AR alone rather than for those with AR + asthma (84.5 vs. 67.5%, $p < 0.001$), whereas NCS were more used to treat patients with both AR and asthma (49.8 vs. 42.4%, $p = 0.01$). GPs did not report any

Table 3. Distribution (number and % of patients) of therapeutic groups prescribed by general practitioners for allergic rhinitis (AR) treatment.

AR treatment	AR alone (n = 776)	AR + asthma (n = 603)	p-value* by χ^2
Anti-H	656 (84.5)	407 (67.5)	<0.001
NCS	329 (42.4)	300 (49.8)	0.01
SCS	67 (8.6)	100 (16.6)	<0.001
LTRAs	24 (3.1)	96 (15.9)	<0.001
Chromones	30 (3.9)	35 (5.8)	0.09
Nasal decongestant	12 (1.5)	6 (1.0)	0.37
SIT	6 (0.8)	—	
Anti-cholinergics	—	2 (0.3)	
Untreated	53 (6.8)	58 (9.6)	0.07

*Statistical difference between patients with AR alone and patients with AR + asthma.

Anti-H, antihistamines; NCS, nasal corticosteroids; SCS, systemic corticosteroids; LTRAs, leukotriene receptor antagonists; SIT, specific immunotherapy.

treatment for 8% of their AR patients (6.8% and 9.6% for patients with AR alone and AR + asthma, respectively).

In 43.6% of AR patients a single drug was prescribed, usually an anti-H, while 39.3% were treated with a two-drug combination (mainly anti-H + NCS), and the remaining 9.1% with more than two drugs (Table 4). The prevalence of treatment with only one drug was significantly ($p < 0.001$) higher in patients with AR alone ($n = 374$, 48.2%) than in those with AR + asthma ($n = 227$, 37.6%); in contrast, a combination of three or more drugs was significantly more prevalent for patients with AR + asthma than for those with AR alone ($n = 75$, 12.4 vs. $n = 50$, 6.4%, $p < 0.001$); there was no difference between the two groups of patients concerning the treatment with a combination of two drugs ($n = 299$, 38.5% for AR alone vs. $n = 243$, 40.3% for AR + asthma, $p = 0.53$) (data not shown).

Figure 1 shows the distribution of different treatments for AR alone or AR + asthma according to ARIA classification. The patients with mild (intermittent or persistent) AR were given mostly a prescription for anti-H + NCS according to the presence of comorbid asthma or a single anti-H according to the absence of comorbid asthma. Combinations of anti-H + NCS or anti-H with other drug/s were the most frequently given treatment for patients with moderate–severe (intermittent or persistent) AR. In a considerable amount of patients with mild intermittent AR a combination therapy of more than one drug was prescribed (39.3% in the AR alone group and 56.4% in the AR + asthma group) and a not insignificant proportion of patients with moderate–severe persistent AR was treated with anti-H as a single drug (29.5% in the AR group and 18.4% in the AR + asthma group).

Using the chi-square test, a significant ($p < 0.001$) relationship between type of treatment (monotherapy, two-drug combination, three or more drugs) and AR severity level (mild or moderate–severe) was shown while no significant association was found according to AR duration (intermittent or persistent).

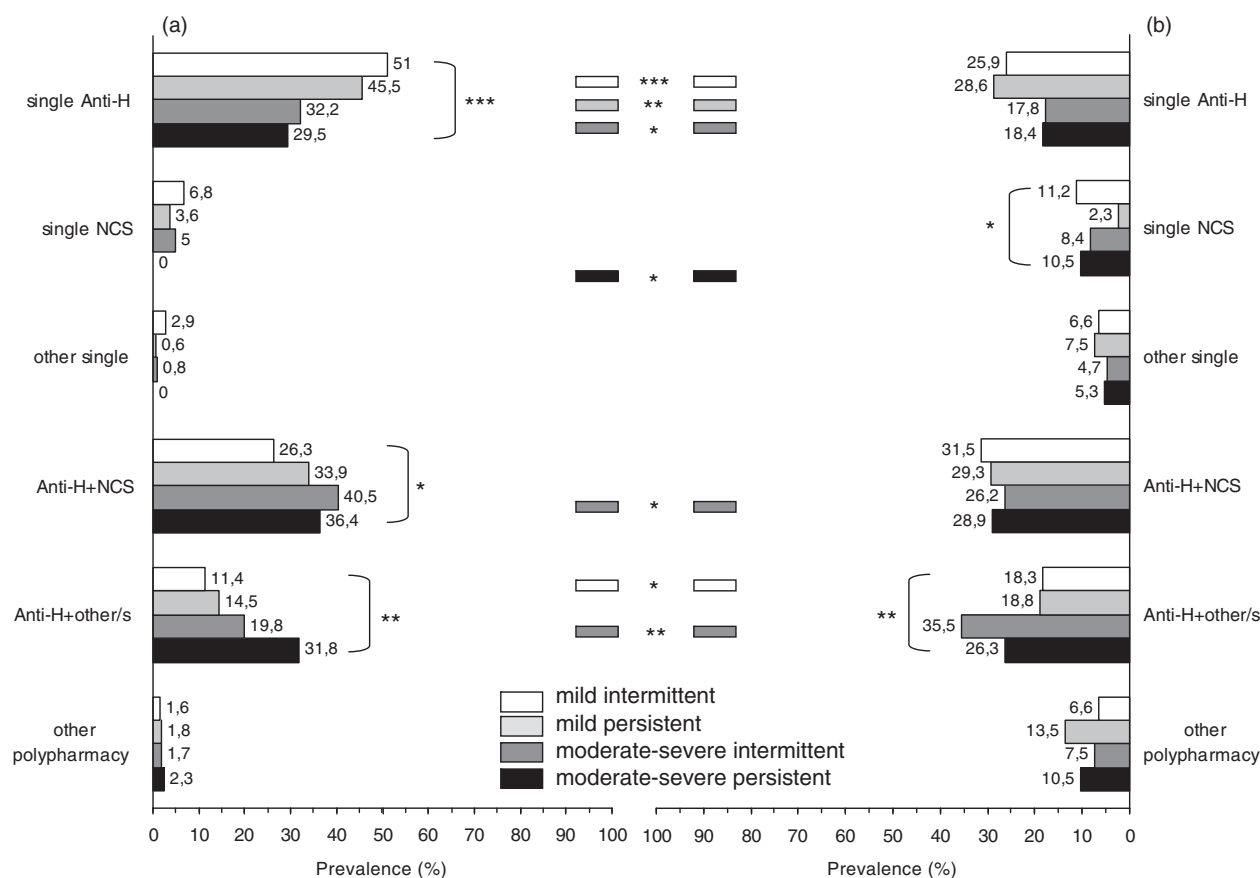
Table 4. Combination of therapeutic groups prescribed by GPs for allergic rhinitis patients ($N = 1379$).

Drug combination	No. of patients	%
Single drug		
Anti-H	457	33.1
NCS	92	6.7
LTRAs	21	1.5
SCS	20	1.5
Decongestant/chromones/SIT	11	0.8
Subtotal	601	43.6
Combination of two drugs:		
Anti-H + NCS	379	27.5
Anti-H + SCS	46	3.3
Anti-H + LTRAs	28	2.0
Anti-H + chromones	23	1.7
NCS + LTRAs	21	1.5
NCS + SCS	17	1.2
Other combination at frequency <1%	28	2.0
Subtotal	542	39.3
Combination of three or more drugs		
Anti-H + NCS + SCS	48	3.5
Anti-H + NCS + chromones	25	1.8
Anti-H + NCS + LTRAs	22	1.6
Other combination at frequency <1%	30	2.2
Subtotal	125	9.1
Untreated	111	8.0

Anti-H, antihistamines; NCS, nasal corticosteroids; LTRAs, leukotriene receptor antagonists; SCS, systemic corticosteroids; SIT, specific immunotherapy.

Prescriptive adherence to ARIA treatment guidelines

Adherence to ARIA guidelines for the treatment of AR was 52%, regardless of severity classification. GPs were generally more compliant with ARIA guidelines in the treatment of patients with AR alone (57.2%) than in those with both AR and asthma (46.3%). GPs adherence to ARIA guidelines in accordance with severity classification was higher in the moderate–severe patients than in the mild ones: the lowest adherence was found for mild intermittent AR (48.5% in the AR alone group and 23.1%



Anti-H, antihistamines; NCS, nasal corticosteroids.

Statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Figure 1. Prevalence of patients treated by GPs for allergic rhinitis (AR) without asthma (a) or with concomitant asthma (b), by treatment and ARIA classification.

in the AR + asthma group, $p < 0.001$), while the highest was for moderate-severe persistent AR (88.6% in the AR alone group and 95% in the AR + asthma) (Table 5).

Discussion

In comparison to AR classification and the suggested treatment proposed by ARIA guidelines, our results indicate over-treatment of mild intermittent AR, as well as under-treatment of moderate-severe persistent AR. Indeed, adherence to ARIA guidelines increases significantly according to disease severity.

Allergic rhinitis treatment

As in previous studies^{16–18}, AR patients were mostly treated with anti-H and NCS, with single or combined therapy. The percentage of patients treated with anti-H (76%) was very close to that found within the Health Search/Thales Database (HSD), an Italian general practice

research database set up by the Italian College of General Practitioners¹⁹: that among 19,789 patients with AR ≥ 18 years of age, around 74% were prescribed anti-H.

Monotherapy was used to treat 43.6% of patients (48% of patients with AR alone), similar to the findings of Antonicelli *et al.* (49% of AR patients)¹⁶. However, a recently published study performed in the USA using administrative claims data from a commercially available database reported that most patients with AR-related prescriptions (78%) were prescribed a single drug²⁰.

Our results highlight that there is substantial use of antihistamines in the treatment of moderate-severe persistent AR whereas ARIA guidelines prefer the use of NCS to reduce inflammation and consequent symptoms. Histamine-mediated events play an important role in the pathophysiology of AR and, as anti-H are able to inactivate histamine receptors, these drugs are considered the preferred first-line treatment for AR²¹. However, it has been demonstrated that anti-H are more effective in seasonal than in perennial AR, but less effective on nasal congestion. For more severe nasal congestion and

Table 5. Prevalence of appropriate prescriptions based on ARIA guidelines for allergic rhinitis (AR) treatment.

Category	AR alone %	AR + asthma %	p-value* by χ^2
Any ARIA classification	57.2	46.3	<0.001
ARIA classification			
Mild intermittent	48.5	23.1	<0.001
Mild persistent	85.0	75.9	0.04
Moderate-severe intermittent	78.9	67.2	0.04
Moderate-severe persistent	88.6	95.0	0.29
p-value† by χ^2	<0.001	<0.001	

*Statistical difference between patients with AR alone and patients with AR + asthma.

†Statistical difference among ARIA categories within the two patient groups.

persistent AR, the treatment with NCS is preferred. NCS are well tolerated, may be taken at high doses, and, differently from systemic corticosteroids (SCS), for long periods with a minimal risk of adverse side-effects^{22,23}. We found that, among the patients with moderate-severe persistent AR, 29.5% of those with AR alone and 18.4% with AR + asthma were given a prescription of anti-H as monotherapy, thus indicating possible under-treatment. A similar result (30.4%) was found in a Belgian study on the management of non-asthmatic AR patients by GPs¹⁷. The decision to prescribe anti-H instead of NCS might be partially explained for reasons of patients' preference and budget. Anti-H are less expensive than NCS. Furthermore, in Italy at the time of the study, long-term prescriptions (≥ 60 days) of antihistamines, unlike NCS, were reimbursed by the National Health System (AIFA, note 89). Among the 12 regions where our GPs were operating, only the Tuscany region has decided to reimburse NCS as from summer 2010, i.e. a few months after the end of our study.

In our study, we show that GPs commonly prescribe NCS as monotherapy or in combination with anti-H in the treatment of mild intermittent AR, although a combination of anti-H + NCS is poorly recommended by ARIA guidelines, at least in severe persistent rhinitis.

We found that about 39% of the patients with mild intermittent AR and without asthma were prescribed a combination therapy, thus indicating possible over-treatment. Moreover, considering the large proportion of mild intermittent patients in this study, the over-treatment in these patients causes an additional cost burden. This result is consistent with the Belgian study by Van Hoecke *et al.*, who reported 33% over-treatment in patients with mild intermittent AR¹⁷. A total of 56.4% of patients with mild intermittent AR with asthma were prescribed a combination therapy; the pathophysiology of concomitant AR and asthma is very complex, and monotherapy may not result in complete relief of the symptoms. A review of available scientific data from clinical trials concluded that combined therapy may produce synergistic benefits for patients with concomitant asthma and AR²⁴.

Our results confirmed previous studies^{16,17,25} which show a positive relationship between the number of prescribed drugs and AR severity. However, duration was found not to be related to disease severity.

The difference between patients with AR alone and with AR + asthma is fairly confusing: while the trend is clear in the first group (decreasing monotherapy with anti-H and increasing combination of anti-H with NCS or others, moving from mild intermittent to severe persistent), the same is not observed in patients with AR + asthma. A possible explanation is that GPs are not strictly focusing on rhinitis in these patients, but rather on asthma treatment.

In general, adherence to ARIA guidelines is quite low¹². The main reason for this seem to be that it is a difficulty for GPs to apply guidelines which are not always clear, while at the same time coping with evidence-based medicine in day-to-day practice¹². However, we found that adherence increased with increasing AR severity and reached high levels for patients with moderate-severe persistent AR (88.6% and 95% of patients with AR alone and AR + asthma, respectively). These are promising results, since there is evidence that the ARIA-based approach for treating patients with persistent AR is the most effective treatment.

Limitations of the study

Our results on the adherence to ARIA guidelines have to be evaluated with caution. Prescription data only provide limited information to judge prescribing quality²⁶, because the prescribed treatment is the result of a doctor/patient agreement and of a specific severity label applied from the GPs to the patient. Despite a broad international consensus on the basic principles for treating allergic rhinitis, different national healthcare systems, economies and medical tradition, may influence actual medical practice and drug prescription attitudes. Therefore, some deviations from the gold standard are to be expected.

At the time the study started, ARIA guidelines recommended the use of leukotriene receptor antagonists

(LTRAs) only for AR patients with concomitant asthma. During the study period, ARIA guidelines were updated and LTRAs were added to the list of recommended drugs regardless of the presence of comorbid asthma². Thus, part of the prescriptions for patients with AR alone which included LTRAs might indeed be adherent to the ARIA guidelines update. In general, very few patients with AR alone were treated with LTRAs. When considering these prescriptions as appropriate, adherence slightly increased, except for the mild intermittent AR group that did not change.

GPs had to actively enroll all their eligible patients with a physician-based diagnosis of allergic rhinitis. The aim of this request was to obtain thorough information about all the rhinitic subjects in the care of Italian GPs. Based on allergic rhinitis prevalence data, coming from other studies¹, a higher number of enrolled rhinitic patients was expected. Such difference could be due to several problems stated by GPs (e.g., lack of time, involvement in other studies, and lack of economic benefit) and to our over-estimation based on the use of epidemiological prevalence rates, quite different from a GPs setting where the number of patients receiving a medical diagnosis turned out to be lower than the number of subjects reporting symptoms in epidemiological surveys. Indeed, an allergic rhinitis prevalence rate of 4.2% from the analyses of the Health Search Database of the Italian College of General Practitioners was reported¹⁹ compared to a prevalence ranging from 16.8 to 25.8% from an Italian epidemiological survey¹. It is possible that our GPs only reported data regarding their regular patients, instead of performing a broader search on their entire databases. However, it should be highlighted that the number of enrolled patients ($N=1379$) was higher than the minimum number of subjects to select, which allowed us to perform analyses with a sufficient statistical power.

Indeed, considering the 4.2% prevalence found by the Health Search Database¹⁹ and the average number of registered citizens for each GP ($n=1300$), it should be pointed out that the 13 rhinitic patients per GP for which we have data, correspond to about 24% of the expected number of 42.

Conclusions

Our results show over-treatment of mild intermittent AR and inappropriate large use of antihistamines to treat moderate-severe persistent AR instead of the recommended NCS. From the clinical implication standpoint, we confirm that GPs do not often follow ARIA guidelines in treating patients with allergic rhinitis, although a promising trend is given by the better adherence in the more severe patients.

Since allergic rhinitis has a huge epidemiological burden and GPs are the first healthcare professionals consulted by patients for their symptoms, our study design could be generalized to a broader setting in Italy and abroad as a monitoring tool for assessing dissemination and implementation of clinical practice guidelines.

Transparency

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