MACVIA clinical decision algorithm in adolescents and adults with allergic rhinitis

Bousquet, Jean
2016-08


http://hdl.handle.net/10138/167445
https://doi.org/10.1016/j.jaci.2016.03.025

Downloaded from Helda, University of Helsinki institutional repository.

This is an electronic reprint of the original article.
This reprint may differ from the original in pagination and typographic detail.
Please cite the original version.
The selection of pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors, including age, prominent symptoms, symptom severity, control of AR, patient preferences, and cost. Allergen exposure and the resulting symptoms vary, and treatment adjustment is required. Clinical decision support systems (CDSSs) might be beneficial for the assessment of disease control. CDSSs should be based on the best evidence and algorithms to aid patients and health care professionals to jointly determine treatment and its step-up or step-down strategy depending on AR control. Contre les
The selection of pharmacotherapy for patients with allergic rhinitis (AR) depends on several factors, such as age, prominent symptoms, symptom severity, control of AR, patient preferences, availability of treatment, and cost. With allergen exposure and the resulting symptoms varying daily, patients with AR would benefit from regular monitoring of their symptoms to facilitate treatment adjustment. Clinical decision support systems (CDSSs) might be beneficial for the accomplishment of this task by assisting health care professionals and patients with clinical decision-making.
tasks. Knowledge-based CDSSs consist of 3 parts: the knowledge base, an inference engine, and a mechanism to communicate. The knowledge base contains the rules and associations of compiled data. The inference engine combines the rules from the knowledge base with the patient’s data. The communication mechanism allows the system to show the results to the user, as well as have input into the system. CDSSs should be based on the best evidence and algorithms to aid patients and health care professionals to jointly determine the treatment and its step-up or step-down strategy depending on AR control. Thus CDSSs should help optimize treatment.

Contre les Maladies Chroniques pour un Vieillissement Actif en Languedoc-Roussillon (MACVIA-LR [fighting chronic diseases for active and healthy ageing], http://macvia.cr-languedocroussillon.fr) is one of the reference sites of the European Innovation Partnership on Active and Healthy Ageing. It initiated the project Integrated Care Pathways for Airway diseases (AIRWAYS ICPs) and the allergy sentinel network MACVIA-ARIA Sentinel Network (MASK). A knowledge-based CDSS is currently being developed to optimize AR control. The communication mechanism of MASK uses interconnected tablets and cell phones. The proposed algorithm of the MACVIA-CDSS is presented in this article.

CONTROL OF AR AND RHINOCONJUNCTIVITIS

In asthmatic patients, the treatment strategy is based on disease control and current treatment. The variability in symptom control is challenging and necessitates careful monitoring, as well as the step up/step down of individualized therapeutic regimens over time. Both long- and short-term maintenance and reliever approaches have been proposed, including the combination of an inhaled corticosteroid and long-acting β-agonist inhaler as maintenance and reliever therapy.

Novartis, and Teva. W. J. Fokkens has received research support from Meda and has received payment for developing a webcast on treatment of rhinitis for general practitioners. J. A. Hanania is on the Boehringer Ingelheim, Mundipharma, and Novartis advisory board; has a patent with AKL Ltd; has received consultancy fees from Novartis; has received research support from Fundação Ciência e Tecnologia and Fundação Calouste Gulbenkian; has received lecture fees from AstraZeneca, Aerocrine, Menarini, GlaxoSmithKline, MSD, and Vitoria; and has received travel support from AstraZeneca and Novartis. T. Keil has received research support from the European Union projects MedDALL and iFAM. P. Kuna has received lecture fees from Adamed, Allergopharma, Almirall, AstraZeneca, GlaxoSmithKline, Hal. Meda, Pfizer, Polpharma, Stallergenes, Lekam, and Bayer and has received lecture fees and is on the advisory board by Boehringer Ingelheim, Celon Pharma, Chiesi, FAES, MSD, Novartis, Polpharma, and Teva. D. Larenas-Linnemann has received consultancy fees from Boehringer Ingelheim, Meda, Pfizer, Mila Pharma, and Chiesi; has received research support from AstraZeneca, MSD, Novartis, Sanofi, UCB, GlaxoSmithKline, Pfizer, MEDA, TEVA, Seneosain, Carmot; has received lecture fees from AstraZeneca, MSD, Novartis, Sanofi, Pfizer, and Meda; has received payment for development of educational presentations from Glenmark; and has received travel support from ALK-Abelló.

K. C. Lodrup Carlsen has received research and travel support from EU MedDALL, is on the Sanofi advisory board, has received research support from National and regional public funding applications. E. O. Melzner has received consultancy fees from AstraZeneca, Boehringer Ingelheim, Church & Dwight, GlaxoSmithKline, Greer, Johnson & Johnson, Meda, Mylan, Regeneron/Sanofi, and Teva; has been employed as a consultant or advisor by Meda, Merck, Mylan, Takeda, and Teva; and has received payment for developing educational presentations from Glenmark. J. Mullol is on the boards for Uricha, Meda, FAES, ALK-Abelló, and Sanofi; has received research support from GlaxoSmithKline, Uricha, FAES, and Meda; and has received lecture fees from Uricha, Harington Pharmaceuticals, Novartis, FAES, Menarini, MSD, Pierre-Fabre, and UCB. A. Muraro has received consultancy fees from Meda. R. N. Nacerio is on the Merck and Sanofi allergy advisory boards, has received consultancy fees from Teva, is employed by the University of Chicago, and has received research support from Meda. S. Palkonen is on the GlaxoSmithKline European Health Advisory Board; has received research support from Air Liquide Sante International, ALK-Abelló, Almirall, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Chiesi, Mundipharma, Sanofi-pasteur, and Stallergenes; has received travel support from Novartis; and declares that she regularly has dialogue with the funding partners listed above, who give unrestricted educational grants to the patient organization, EFA, for which she works as a Director. N. Papadopoulos has received research support from GlaxoSmithKline, Sterne, and Merek; and has received payment for developing educational presentations from Abbvie, Sanofi, Menarini, and Meda; has received consultancy fees from GlaxoSmithKline, Abbvie, Novartis, Menarini, Meda, and ALK-Abelló; and has received lecture fees from Allergopharma, Uricha, GlaxoSmithKline, Stallergenes, and MSD. D. Price is on the boards for Aerocrine, Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, and Teva; has received consultancy fees from Almirall, Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Eli Lilly, GlaxoSmithKline, Meda, Merck, Mundipharma, Napp, Novartis, Oron, Pfizer, Respiratory Effectiveness Group, Takeda, Teva, Zentiva; has received lecture fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GlaxoSmithKline, Kyorin, Meda, Merck, Mundipharma, Novartis, Pfizer, SkyelPharma, Takeda, and Teva; has received payment for manuscript preparation and editing from Mundipharma and Teva; has a patent with AKL Ltd; has received payment for developing educational presentations from GlaxoSmithKline and Novartis; has stock in AKL Ltd; has received travel support from Aerocrine, Boehringer Ingelheim, Mundipharma, Napp, Novartis, and Teva; has received funding for patient enrolment or completion of research from Almirall, Chiesi, Teva, and Zentiva; has served as a peer reviewer for grant committees for the Medical Research Council, Efficacy and Mechanism Evaluation Programme, and HTA; and is 80% owner of Research in Real Life, which receives unrestricted funding for investigator-initiated studies from Aerocrine, AKL Ltd, Almirall, Boehringer Ingelheim, Chiesi, Meda, Mundipharma, Napp, Novartis, Orison, Takeda, Teva, and Zentiva. D. Ryan is on the Boards for Stallergenes and Uricha; has received consultancy fees from Meda; is employed by Optimum Patient Care and University of Edinburgh; has received lecture fees from Meda, Chiesi, Teva, AstraZeneca, and Boehringer Ingelheim; has received payment for developing educational presentation from Meda; and is Chairman of the European Academy of Allergy and Clinical Immunology (EAACT) Primary Care Interest Group. A. Valulius is a board member without financial interest of the nonprofit organizations the European Academy of Paediatrics, European Paediatric Association, European Confederation of Primary Care Paediatricians, Lithuanian Paediatric Society, and Lithuanian Paediatric Respiratory Society; has received research support from European Union Social Fund and Lithuanian Ministry of Health; has received travel support from the European Academy of Pediatrics; is Chairman of Executive Board of IPOKRaTES Lithuania Fund. E. Volwirta has received travel support from Stallergenes. M. Wickman has received research support and lecture fees from Thermo Fisher, has received consultation fees from Thermo Fisher and Microtest Ds, and has received payment for developing educational presentations from Stallergenes. T. Zuberbier has received consultancy fees from Ansell, Bayer Schering, DST, FAES, Fujisawa, HAL, Henkel, Keyolyn, Leti, Menarini, Merck, MSD, Novartis, Pooster & Gamble, Ranbaxy, Sanofi-Aventis, Schering Plough, Stallergenes, Takeda, and UCB; is on the German Society for Allergy and Clinical Immunology Scientific Advisory Board; is head of the European Centre for Allergy Research Foundation; is a World Health Organization Initiative Allergic Rhinitis and its Impact on Asthma committee member; is a member of the World Allergy Organization Communications Council; and is Secretary General of the Global Allergy and Asthma European Network. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 30, 2015; revised February 5, 2016; accepted for publication March 15, 2016. Available online April 23, 2016.

Corresponding author: Jean Bousquet, MD, CHRU Arnaud de Villeneuve, Département de Pneumologie, 371 Avenue du Doyen Gaston, Giraud, 34295 Montpellier Cedex 5, France. E-mail: jean.bousquet@orange.fr.

The CrossMark symbol notifies online readers when updates have been made to the article such as errata or minor corrections 0901-6749 © 2016 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).http://dx.doi.org/10.1016/j.jaci.2016.03.025
The treatment of AR also requires the consideration of (1) the type (rhinitis, conjunctivitis, and/or asthma) and severity of symptoms, (2) the relative efficacy of the treatment, (3) the speed of onset of action of treatment, (4) current treatment, (5) historic response to treatment, (6) patient’s preference, (7) interest to self-manage, and (8) resource use. Guidelines and various statements by experts for AR pharmacotherapy usually propose the approach summarized in Box 1.28-46

**Box 1. Summary of recommendations for the treatment of AR and conjunctivitis used in the algorithm**

- Oral or intranasal H1-antihistamines are less effective than intranasal corticosteroids for the control of all rhinitis symptoms.28-33
- Leukotriene receptor antagonists are usually considered less effective than oral H1-antihistamines.30,34,35
- Comparisons between oral and intranasal H1-antihistamines differ between recommendations, and thus no definite conclusions have yet been reached.
- Combined intranasal fluticasone propionate and azelastine hydrochloride in a single device is more effective than monotherapy and is indicated for patients when monotherapy with either an intranasal H1-antihistamine or glucocorticoid is considered inadequate.1,34-37
- Intranasal antihistamines and intranasal corticosteroids are effective for ocular symptoms, with no significant difference between them.38,39 However, the combination of azelastine and fluticasone propionate was more effective than fluticasone propionate alone.36,37
- In most studies, combinations of oral antihistamines or leukotriene receptor antagonists and intranasal corticosteroids are in general not more effective than monotherapy with intranasal corticosteroids.30,41
- Intraocular H1-antihistamines or cromones are effective for ocular symptoms.42 The importance of decongestants is debatable.26 However, the efficacy of treatment varies with individual patient response.
- In clinical practice, intranasal corticosteroids need a few days to be fully effective, whereas intranasal H1-antihistamines or combined intranasal fluticasone and azelastine are rapidly effective.43
- All recommended medications are considered safe at the usual dosage. First-generation oral H1-antihistamines are sedating and should be avoided.34
- Oral or nebulized corticosteroids can be helpful in patients with severe disease whose symptoms are uncontrolled by other treatment, although studies are lacking in patients with AR.45
- Further studies are needed in preschool children to make more firm recommendations possible, although recent studies show the efficacy of oral H1-antihistamines.46

PATIENTS’ VIEWS

Many patients with AR are not satisfied with their current treatment,52-54 and this results in frequent nonadherence to therapy.55,56 In some studies, most patients were satisfied with their treatment, but full control was rarely achieved.54-57,58 Despite the vast availability of treatment options, most patients are “very interested” in finding a new medication,56,60 and around 25% are “constantly” trying different medications to find one that “works.”56 Patients want more effective treatments that can control all their symptoms, including ocular ones,61,62 and a more rapid onset of action.63

Some patients believe that their health care provider does not understand their allergy treatment needs or does not take their allergy symptoms seriously.52 Many patients self-medicate with over-the-counter drugs for a long period of time and usually only consult a physician when their treatment is ineffective.56 In one study, patients chose a step-down therapy to speed up the control of symptoms.64

A patient’s individual preference for an oral or intranasal route treatment needs to be considered.52,64,65 In addition, health care professionals need to inform the patient of the relative benefits and harms of each prescribed treatment to support their decision making.
ALGORITHM DECISION AID

A step-up/step-down individualized approach to AR pharmacotherapy might hold the potential for optimal control of AR symptoms while minimizing side effects and costs. However, the following should be considered:

- as in asthmatic patients, treated and untreated patients should be considered differently (Figs 1 and 2);
- most patients have received a previous treatment that should guide health care professionals with regard to the current prescription; and
- patterns of medication use in previously treated patients should be evaluated when future treatment is initiated.

The step-up or step-down strategy should be discussed with the patient and should consider the following:

- efficacy of previous treatments;
- adherence to treatment;
- the patient’s preference (route of administration, fear of side effects, and experience of the patient regarding the treatment);
- possible side effects or harms; and
- costs.

The step-up approach consists of the following:

- **Step 1:** For mild symptoms, use intranasal or oral nonsedating H<sub>1</sub>-antihistamines.
- **Step 2:** For moderate-to-severe symptoms and/or persistent AR, use intranasal corticosteroids. The dose of some intranasal corticosteroids can be increased according to the package insert.
- **Step 3:** For patients with uncontrolled symptoms at step 2 (current or historical), use a combination of intranasal corticosteroids and intranasal H<sub>1</sub>-antihistamines. However, depending on the physician’s experience, other therapeutic strategies can be used.
- **Step 4:** It is possible that an additional short course of oral steroids might help to establish control and continue control by step 3. Intraocular cromones or H<sub>1</sub>-antihistamines can be added to improve the control of ocular symptoms.
- Treatment should be reassessed quickly (eg, 1-7 days) to confirm control by using a step-up approach.
- Patients whose symptoms are uncontrolled at step 3 should be considered as having severe chronic upper airway disease and might benefit from specialist referral and assessment for allergy workup and nasal examination. For example, specialist referral should be considered if there is failure to reduce the VAS score to less than 5 of 10 after 10 to 14 days, assuming the patient is adherent to therapy.
- At all times, patient adherence and intranasal device technique mastery should be regarded as potential for lack of treatment effect.

Alternatively, a step-down approach can be used, and step 3 treatment should be considered as the first option in patients with a previous treatment failure or resistance to monotherapy. After a few days of achieving complete control, consideration could be given to treatment reduction. However, the step-down approach is based on consensus, and more data are needed.

The duration of treatment is determined by the type of rhinitis (intermittent or persistent). In the patient with intermittent rhinitis, treatment should be continued daily for 2 weeks or for the duration of the pollen season or other specific allergen exposure. In the patient with persistent rhinitis, a longer course

---

**FIG 1.** Step-up algorithm in untreated patients using the VAS (adolescents and adults). The proposed algorithm considers the treatment steps and patient preference and VAS levels in ratio. If ocular symptoms remain, add intraocular treatment.
Assessment of control in treated symptomatic patient

**REFERENCES**


RATIONAL FOR USING A VAS IN THE ALGORITHM

Certain differences between groups in their VAS scores or changes in scores might have no clinical relevance, even if they achieve statistical significance. A wide range of minimal clinically important differences (MCIDs) in change scores on the pain VAS have been reported by using different methods. MCIDs ranged from 9 to 30 mm (of 100 mm) in emergency departments. In other settings, changes of 33% and 31 mm have been shown to be clinically meaningful. In patients with endometriosis, the pain MCID was set at 10 mm. The MCID for the fatigue VAS was around 10 mm in a large rheumatoid arthritis clinical practice and similar to that seen in clinical trials. The MCID in the VAS pain score does not differ with sex, age, and cause-of-pain groups or with the severity of pain being experienced. However, the linearity of the pain VAS is found in some but not all studies. Pain VAS measurement error has been reported to be up to 20 mm.

Consequently, change scores and the calculations of aspects, such as MCIDs, can be carefully considered by the potential lack of interval scaling of the VAS and further compromised by the magnitude of measurement error. Repeated pain VAS data meet the strict requirements of the Rasch model, including unidimensionality, and they were internally valid. However, the pain VAS does not behave linearly, and the MCID can underestimate or overestimate true change during repeated pain VAS.

In patients with AR, to our knowledge, there is a single study that has estimated MCMDs in the VAS during treatment. By using receiver operating characteristic curve analysis, an appropriate method for estimation of MCMDs, the established cutoff variation of 23 mm for the VAS was associated with a cutoff variation of 0.5 for the Rhinocoeactinities Quality of Life Questionnaire (RQLQ). Sensitivity analysis with RQLQ and Total Symptom Score 6 scales confirmed the aptitude of the cutoff value (23 mm) to discriminate changes in symptoms and QOL. The MCMD was the same whatever the baseline VAS level. A level of more than 23 mm appears to be a relevant cutoff. VAS changes appear to encompass both symptoms and disease-specific QOL. Another study, the Control of Allergic Rhinitis and Asthma Test, approximated the VAS MCMD. In CARAT, the MCID is 4 (range, 0-30).

The real-life study of Demoloy et al. in primary care used the same methods as a cluster randomized trial carried out in specialist practices. Both studies, which were carried out in France in large populations, showed a very similar change in VAS levels during treatment depending on total symptom scores and RQLQ scores. These studies suggest that the cutoff of 23 mm is appropriate to find a clinically significant difference.

VAS levels appear to be similar in different countries in patients with severe intermittent or persistent rhinitis. A VAS can be used in all age groups, including preschool children (guardian evaluation) and the elderly. Furthermore, it can be used in a wide variety of languages. VAS levels vary with the Allergic Rhinitis and its Impact on Asthma classification in many languages. A VAS level of 50 (>100 mm) is suggestive of moderate-to-severe AR, although in some studies the cutoff was greater than 60 mm. AVAS was used to define severe chronic upper airway disease. Thus the MCDI found in 2 large French populations can be generalized to other countries with different languages and cultures across the lifecycle. However, future studies should refine this cutoff level.

REFERENCES


