

Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision

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Background: Allergic rhinitis (AR) affects 10% to 40% of the population. It reduces quality of life and school and work performance and is a frequent reason for office visits in general practice. Medical costs are large, but avoidable costs associated with lost work productivity are even larger than those incurred

by asthma. New evidence has accumulated since the last revision of the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines in 2010, prompting its update.

Objective: We sought to provide a targeted update of the ARIA guidelines.

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Methods: The ARIA guideline panel identified new clinical questions and selected questions requiring an update. We performed systematic reviews of health effects and the evidence about patients' values and preferences and resource requirements (up to June 2016). We followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence-to-decision frameworks to develop recommendations.

Results: The 2016 revision of the ARIA guidelines provides both updated and new recommendations about the pharmacologic treatment of AR. Specifically, it addresses the relative merits of using oral H₁-antihistamines, intranasal H₁-antihistamines, intranasal corticosteroids, and leukotriene receptor antagonists either alone or in combination. The ARIA guideline panel provides specific recommendations for the choice of treatment and the rationale for the choice and discusses specific considerations that clinicians and patients might want to review to choose the management most appropriate for an individual patient.

Conclusions: Appropriate treatment of AR might improve patients' quality of life and school and work productivity. ARIA recommendations support patients, their caregivers, and health care providers in choosing the optimal treatment. (*J Allergy Clin Immunol* 2017;■■■:■■■-■■■.)

Key words: Allergic rhinitis, practice guideline

Allergic rhinitis (AR) is among the most common diseases globally and usually persists throughout life.¹ The prevalence of self-reported AR has been estimated to be approximately 2% to 25% in children² and 1% to greater than 40% in adults.^{1,3} The prevalence of confirmed AR in adults in Europe ranged from 17% to 28.5%. Recent studies show that the prevalence of AR has increased in particular in countries with initial low prevalence (for a discussion of prevalence of AR, see section 5.1-5.2 in Allergic Rhinitis and its Impact on Asthma [ARIA] 2008 Update¹). Classical symptoms of AR are nasal itching, sneezing, rhinorrhea, and nasal congestion. Ocular symptoms are also frequent; allergic rhinoconjunctivitis is associated with itching and redness of the eyes and tearing. Other symptoms include itching of the palate, postnasal drip, and cough.

AR is also frequently associated with asthma, which is found in 15% to 38% of patients with AR,^{4,5} and nasal symptoms are present in 6% to 85% patients with asthma.⁶⁻⁹ In addition, AR is a risk factor for asthma,^{4,9} and uncontrolled moderate-to-severe AR affects asthma control.^{10,11}

Compared with other medical conditions, AR might not appear to be serious because it is not associated with severe morbidity and mortality. However, the burden and costs are substantial.¹² AR reduces the quality of life of many patients, impairing sleep quality and cognitive function and causing irritability and fatigue. AR is associated with decreased school and work performance, especially during the peak pollen season.¹ AR is a frequent reason for general practice office visits. Annual direct medical costs of AR are substantial, but indirect costs associated with lost work productivity are greater than those incurred by asthma.¹³⁻¹⁵ Appropriate treatment of AR improves symptoms, quality of life, and work and school performance.

Clinical practice guidelines for AR management were developed over the past 20 years¹⁶ and have improved the care of

Abbreviations used

AR:	Allergic rhinitis
ARIA:	Allergic Rhinitis and its Impact on Asthma
EtD:	Evidence to decision
GRADE:	Grades of Recommendation, Assessment, Development, and Evaluation
ICP:	Integrated care pathway
PAR:	Perennial allergic rhinitis
SAR:	Seasonal allergic rhinitis
SMD:	Standardized mean difference

patients with AR.¹⁷ However, transparent reporting of guidelines to facilitate understanding and acceptance are needed. The ARIA initiative was initiated during a World Health Organization workshop in 1999¹⁸ and updated in 2008.¹ The ARIA 2010 revision was the first evidence-based guideline in allergy to follow the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach¹⁹ with no influence of for-profit organizations and an explicit declaration and management of potential competing interests of panel members.²⁰ It summarized the potential benefits and harms underlying the recommendations, as well as assumptions around values and preferences that influenced the strength and direction of the recommendations. In 2014, the ARIA revision was found to rank first in the rigor of development and quality of reporting of guidelines about the management of AR,¹⁶ although recent guidelines published later were not considered.²¹

CLINICAL QUESTIONS

Since the last revision of the ARIA guidelines in 2010,²⁰ new treatments have become available, and new evidence has accumulated about selected other treatments. By using a modified Delphi process, the ARIA guideline panel selected new questions that required answering with recommendations or the existing recommendations that required an updated review of the evidence and potentially updating the recommendations themselves. Therefore this revision of the ARIA guidelines is limited in scope and addresses 6 questions about the treatment of AR:

1. Should a combination of oral H₁-antihistamine and intranasal corticosteroid versus intranasal corticosteroid alone be used for treatment of AR?
2. Should a combination of intranasal H₁-antihistamine and intranasal corticosteroid versus intranasal corticosteroid alone be used for treatment of AR?
3. Should a combination of an intranasal H₁-antihistamine and an intranasal corticosteroid versus intranasal H₁-antihistamine alone be used for treatment of AR?
4. Should a leukotriene receptor antagonist versus an oral H₁-antihistamine be used for treatment of AR?
5. Should an intranasal H₁-antihistamine versus an intranasal corticosteroid be used for treatment of AR?
6. Should an intranasal H₁-antihistamine versus an oral H₁-antihistamine be used for treatment of AR?

The target audience of these guidelines is primary care clinicians, school nurses, pharmacists, specialists in allergy and clinical immunology, general internists managing patients with AR, and pediatricians. Ear-nose-throat specialists, other health

care professionals, and health care policy makers can also benefit from these guidelines.

CLASSIFICATION OF AR

The classification of AR was revised by ARIA in 2001. A major change was the introduction of the terms “intermittent” and “persistent.”¹⁸ Before then, AR was classified, based on the time and type of exposure and symptoms, into seasonal allergic rhinitis (SAR; most often caused by outdoor allergens, such as pollens or molds), perennial allergic rhinitis (PAR; most frequently, although not necessarily, caused by indoor allergens such as house dust mites, molds, cockroaches, and animal dander), and occupational allergic rhinitis.^{22,23} With very few exceptions, published studies refer to SAR and PAR and enroll patients based on the offending allergen (pollen, house dust mites, or both), and we retained the terms SAR and PAR to enable the interpretation of published evidence.

The recommendations in the ARIA 2016 update apply directly to patients with moderate-to-severe AR. They might be less applicable to treatment of patients with mild AR who frequently do not seek medical help and manage their symptoms themselves with medications available over the counter.

RECOMMENDATIONS FOR CHILDREN

Almost all studies used to answer the questions in this update of the ARIA guidelines included exclusively adult patients. However, careful extrapolation to the pediatric population can be attempted. One can assume that the relative effects of treatment of AR are likely similar among adults and children, but adverse effects might be more or less frequent, and their perception and importance might be different (eg, bitter taste). Values and preferences for specific outcomes and treatments can also vary between adults and children.

METHODOLOGY

The full description of methods used to develop recommendations in these guidelines is described in the [Methods](#) section of the full version of the guideline document (see [Online Repository item E1](#) in this article's Online Repository at www.jacionline.org). Here we describe briefly the methodology to facilitate the interpretation of the guidelines.

Questions and outcomes of interest

The scope and questions for this update of the ARIA guidelines were identified by the ARIA guideline panel members. The guideline panel deemed the following outcomes to be important to patients: nasal and ocular symptoms, quality of life, work/school performance, and adverse effects. As for the previous revision of the ARIA guidelines, we did not formally assess the relative importance of each outcome of interest (ie, which outcomes are more and which are less important) but rather adopted the rating agreed upon by the guideline panel according to the structured discussion.²⁴ In general, combined nasal symptoms, ocular symptoms, quality of life, work/school performance, and serious adverse effects were considered critical to the decision, and individual symptoms, a composite outcome of any adverse effects and adverse effects that were not serious or did

not lead to discontinuation of treatment, were considered important but not critical (see evidence profiles in [Online Repository item E2](#) in this article's Online Repository at www.jacionline.org).

Evidence review and development of clinical recommendations

For each question, the methodology group performed a full systematic review of the literature to identify and summarize evidence about the effects of interventions on the outcomes of interest. We also searched systematically for information about patients' values and preferences and resource use (cost). We systematically searched the Medline, Embase, and Cochrane CENTRAL electronic databases. Titles and abstracts and subsequently full-text articles were screened in duplicate to assess eligibility according to prespecified criteria. Panel members were contacted to confirm completeness of the body of evidence and suggest additional articles that might have been missed in electronic searches.

To obtain the estimates of effects on each outcome of interest, we performed meta-analyses using the Cochrane Collaboration Review Manager Software, version 5.3.5.²⁵ We prepared evidence summaries (see [Online Repository item E2](#)) for each question according to the GRADE approach¹⁹ by using the GRADEpro Guideline Development Tool online application (www.gradepro.org).

When continuous outcomes (eg, symptom scores or quality of life) are measured by using different scales, the results can only be combined in meta-analysis by using the standardized mean difference (SMD), which is expressed in SD units.²⁶ Results expressed as an SMD are challenging to interpret. To facilitate understanding, we used interpretation of the effect size according to Cohen conventional criteria²⁷: an SMD of around 0.2 is considered a small effect, an SMD of around 0.5 is considered a moderate effect, and an SMD of around 0.8 or higher is considered a large effect. We used this interpretation throughout this document when we referred to effects of interventions as small, moderate, or large.

We assessed the risk of bias at the outcome level by using the Cochrane Collaboration's risk of bias tool.²⁸ Subsequently, we assessed the certainty of the body of evidence (ie, confidence in the estimated effects, which is also known as “quality of the evidence”) for each of the outcomes of interest according to the GRADE approach²⁹ based on the following criteria: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of a dose-effect relationship, and assessment of the effect of residual opposing confounding. Certainty of the evidence was categorized into 4 levels: high, moderate, low, and very low.

For each question, we summarized all information in evidence-to-decision (EtD) frameworks (see [Online Repository item E2](#)) that included concise description of desirable and undesirable health effects, certainty of the evidence about those effects, evidence and assumptions about patients' values and preferences, required resources and cost-effectiveness, potential influence on health equity, acceptability of the intervention to various stakeholders, and feasibility of implementation.³⁰ Judgments about all these factors and suggested recommendations in EtD frameworks were drafted by J.L.B., who was also a clinical expert.

EtDs for all questions were reviewed by the ARIA guideline panel members, who provided feedback by means of electronic communication and during a face-to-face meeting of Integrated Care Pathways for Airway Diseases (AIRWAYS ICPs)^{31,32} and Frailty European Innovation Partnership on Active and Healthy Ageing Reference Sites in Lisbon, Portugal on July 1, 2015.³³ All comments were addressed, and the frameworks were modified accordingly. Modified EtD frameworks that included judgments about the research evidence, additional considerations of ARIA panel members, and draft recommendations were sent to all ARIA panel members for review and approval or disapproval and comments by using the online SurveyMonkey software (www.surveymonkey.com). We recorded and addressed all agreements/disagreements, comments, and suggestions for changes. We present the final EtD frameworks in [Online Repository item E2](#).

Recommendations and their strength were decided by consensus. The ARIA guideline panel agreed on the final wording of recommendations and remarks with further qualifications for each recommendation. The final document, including the recommendations, was reviewed and approved by all members of the guideline panel.

According to the GRADE approach, the recommendations can be either “strong” or “conditional” depending on the guideline panel’s confidence that following the recommendation would bring more good than harm to patients. The wording of recommendations reflects their strength, and one can use the terms “we recommend” for strong recommendations and “we suggest” for conditional recommendations. [Box 1](#) provides suggested interpretation of strong and conditional recommendations.

Recommendations

We present all recommendations in [Table I](#). We provide the rationale for the recommendations and the consideration of all factors that influenced the recommendations: effects on all important health outcomes, certainty of the available evidence, values and preferences, acceptability by stakeholders, requirements for resources, feasibility, and any issues of health equity in the unabridged guideline document in [Online Repository item E1](#). Detailed summaries of the evidence supporting each recommendation and the guideline panel judgements are shown in [Online Repository item E2](#).

How to use these guidelines

The ARIA guidelines about treatment of AR are not intended to impose a standard of care for individual countries. They provide the basis for rational informed decisions for patients, parents, clinicians, and other health care professionals. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should not view these recommendations as dictates. Recommendations provide guidance for typical patients; no recommendation can take into account all of the often-compelling unique individual circumstances. Thus, no one charged with evaluating health care professionals’ actions should apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements regarding the underlying values and preferences, as well as qualifying remarks accompanying each recommendation,

Box 1. Strength of recommendation

Strong recommendation

For patients: Most patients in this situation would want the recommended course of action, and only a small proportion would not.

For clinicians: Most patients should receive the intervention. Adherence to a strong recommendation could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help patients make decisions consistent with their values and preferences.

For health care policy makers: The recommendation can be adopted as a policy or performance measure in most situations.

Conditional recommendation

For patients: The majority of patients in this situation would want the suggested course of action, but many would not.

For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids might be useful in helping patients to make decisions consistent with their values and preferences.

For health care policy makers: Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (eg, shared) decision-making processes can serve as a performance measure.

should never be omitted when quoting or translating recommendations from these guidelines.

CONCLUSIONS

Evidence-based guidelines are at the cornerstone of integrated care pathways (ICPs),^{31,32} structured multidisciplinary care plans that promote translation of guideline recommendations into local protocols and their subsequent application in clinical practice. Usually, several guidelines are available providing advice about the management of the same condition.¹⁶ It is important to wisely choose appropriate guidelines for local adaptation and creation of ICPs because most of them have limitations because of either the development of the guideline itself or the available research evidence and its interpretation. The most common limitations of guidelines in AR are narrowness in scope (addressing only a small selection of important questions about the management of a given condition), suboptimal rigor of development and reporting, and inadequate representation of the views of patients and their caregivers.¹⁶ We acknowledge that for the ARIA 2016 update, we have not reviewed all recommendations from the ARIA 2010 guidelines. However, we updated only 3 recommendations suggested by the ARIA panel members as requiring the update, and we addressed 3 new questions. We also acknowledge that the ARIA guideline panel included allergists, ear-nose-throat specialists, pulmonologists, general practitioners, and pediatricians but did not include other health care professionals, pharmacists, and patients themselves. However, for the ARIA 2016 update, we systematically searched and reviewed the published evidence about the patients’ values and preferences regarding the outcomes and treatments for AR that to certain degree helped to overcome this limitation. We summarized the results in the section about the assumed

TABLE I. Recommendations

Recommendation	Assumed values and preferences	Explanations and other considerations
Question 1: Should a combination of an oral H₁-antihistamine (OAH) and intranasal corticosteroid (INCS) vs INCS alone be used for treatment of AR?		
Recommendation 1A: In patients with SAR, we suggest either a combination of an INCS with an OAH or an INCS alone (conditional recommendation low certainty of evidence).	ARIA guideline panel acknowledged that the choice of treatment would depend mostly on patient preferences and local availability and cost of treatment. Panel members assumed that in the majority of situations, potential net benefit would not justify spending additional resources.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. In settings in which the additional cost of an OAH is not large and/or patients' values and preferences differ from those assumed by guideline panel members, a combination therapy might be a reasonable choice, especially in patients whose symptoms are not well controlled with an INCS alone, those with pronounced ocular symptoms, or those commencing treatment because of likely faster onset of treatment effects. This recommendation concerns regular use of newer and less sedative OAHs and INCSs in patients with SAR. For older OAHs with more sedative effects, the balance of desirable and undesirable effects may be different.
Recommendation 1B: In patients with PAR, we suggest an INCS alone rather than a combination of an INCS with an OAH (conditional recommendation very low certainty of evidence).	—	Currently available evidence suggests that there is no additional benefit from a combination therapy compared with INCS alone, and there might be additional undesirable effects. This recommendation is conditional because of sparse information and thus very low certainty of the estimated effects.
Question 2: Should a combination of an intranasal H₁-antihistamine (INAH) and INCS vs an INCS alone be used for treatment of AR?		
Recommendation 2A: In patients with SAR, we suggest either a combination of an INCS with an INAH or an INCS alone (conditional recommendation moderate certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment. At initiation of treatment (approximately the first 2 weeks), a combination of an INCS with an INAH might act faster than an INCS alone and thus might be preferred by some patients.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. In settings in which the additional cost of combination therapy is not large and/or patients value potential benefits more than any increased risk of adverse effects, a combination therapy might be a reasonable choice.
Recommendation 2B: In patients with PAR, we suggest either a combination of an INCS with an INAH or an INCS alone (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation because of the very low certainty of the evidence. At the initiation of treatment (approximately the first 2 weeks), combination of an INCS with an INAH might act faster than an INCS alone and thus might be preferred by some patients.
Question 3: Should a combination of an INAH and INCS vs an INAH alone be used for treatment of AR?		
Recommendation 3A: In patients with SAR, we suggest a combination of an INCS with an INAH rather than an INAH alone (conditional recommendation low certainty of evidence).	This recommendation places higher value on additional reduction of symptoms and improved quality of life with a combination therapy compared with an INAH alone. It places a lower value on avoiding additional cost (expenditure of resources).	This is a conditional recommendation, and thus different choices will be appropriate for different patients. In settings in which the additional cost of a combination therapy is large, an alternative choice (ie, and INAH alone) might be equally reasonable. One panel member thought that the recommendation should be conditional for either the intervention or comparison.
Question 4: Should a leukotriene receptor antagonist (LTRA) vs an OAH be used for treatment of AR?		
Recommendation 4A: In patients with SAR, we suggest either an LTRA or an OAH (conditional recommendation moderate certainty of evidence).	Panel members acknowledged that the choice of an LTRA or OAH will mostly depend on patient preferences and local availability and cost of specific medications. In many settings an OAH might still be more cost-effective, but this will largely depend on availability of generic LTRAs and the local cost of various newer-generation OAHs and LTRAs.	Some patients with AR who have concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from an LTRA more than from an OAH. However, this recommendation applies to treatment of AR but not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.

(Continued)

TABLE I. (Continued)

Recommendation	Assumed values and preferences	Explanations and other considerations
Recommendation 4B: In patients with PAR, we suggest an OAH rather than a LTRA (conditional recommendation low certainty of evidence).	This recommendation places a higher value on possibly larger improvement of symptoms and quality of life with an OAH compared with an LTRA. It places a lower value on possible increased risk of somnolence.	This is a conditional recommendation, and thus different choices will be appropriate for different patients based on their preferences for reduction of symptoms vs avoiding the risk of adverse effects. This might be more important for patients with PAR than those with SAR because they might use those medications for longer periods of time. Some patients with AR and concomitant asthma, especially exercise-induced and/or aspirin-exacerbated respiratory disease, might benefit from an LTRA more than from an OAH. However, this recommendation applies to treatment of AR but not to treatment of asthma. Patients with asthma who have concomitant AR should receive an appropriate treatment according to the guidelines for the treatment of asthma.
Question 5: Should an INAH vs an INCS be used for treatment of AR?		
Recommendation 5A: In patients with SAR, we suggest an INCS rather than an INAH (conditional recommendation moderate certainty of evidence).	This recommendation places a higher value on likely small but greater reduction of symptoms and improvement of quality of life with an INCS compared with an INAH and a lower value on avoiding larger cost of treatment with an INCS in many jurisdictions.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his values and preferences, considering local availability and costs.
Recommendation 5B: In patients with PAR, we suggest an INCS rather than an INAH (conditional recommendation low certainty of evidence).	This recommendation places a higher value on probably greater reduction of nasal symptoms with an INCS compared with an INAH, although the overall difference is likely small. It places a lower value on avoiding larger cost of treatment with an INCS in many jurisdictions.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his values and preferences, considering local availability and costs.
Question 6: Should an INAH vs an OAH be used for treatment of AR?		
Recommendation 6A: In patients with SAR, we suggest either an INAH or OAH (conditional recommendation low certainty of evidence).	The panel members acknowledged that the choice of treatment will depend mostly on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.
Recommendation 6B: In patients with PAR, we suggest either an INAH or OAH (conditional recommendation very low certainty of evidence).	The panel members acknowledged that the choice of treatment will mostly depend on patient preferences and local availability and cost of treatment.	This is a conditional recommendation, and thus different choices will be appropriate for different patients. Clinicians must help each patient to arrive at a decision consistent with her or his preferences, considering local availability, coverage, and costs.

INAH, Intranasal H₁-antihistamine; INCS, intranasal corticosteroid; LTRA, leukotriene receptor antagonist; OAH, oral H₁-antihistamine.

values and preferences in the full text of the ARIA 2016 update (see [Online Repository item E1](#)) and in the relevant sections of EtD tables (see [Online Repository item E2](#)).

The available evidence has important limitations: (1) selective measurement and reporting of outcomes (eg, few studies properly measure and report quality of life, which is the most important outcome in patients with AR), (2) selection of patients for clinical trials that might not represent appropriately the patients seen in primary care,³⁴ and (3) not distinguishing between patients with different age or severity of symptoms (lack of proper stratification),³⁵ thus limiting the applicability and generalizability of the research findings. Given these limitations, clinical practice guidelines, especially those with international audience, should emphasize rigorous systematic review of the health effects and explicit and detailed description of the assumed values and

preferences and considerations of cost, feasibility, acceptability, and health equity issues because it is currently following the GRADE EtD frameworks.³⁶⁻³⁸ Such detailed, explicit, and transparent reporting of guidelines facilitates local adaptation of recommendations and their translation into ICPs. Systematic and transparent summaries of the evidence clearly identifying gaps in available research evidence are needed to direct the research agenda and to avoid unnecessary expenditure of resources for further clinical research when it is not necessary.³⁹

Implementation of guidelines in different settings and countries depends on the availability of health interventions (eg, medical tests, medications, and equipment), availability of resources, and cultural differences, among others. Thus local adaptation of recommendations can be required, and ICPs need to be developed at the national, regional, or local level. However,

they should always be based on systematically reviewed evidence of desirable and undesirable consequences. The ARIA 2016 revision will be used to develop the ICPs proposed by the European Innovation Partnership on Active and Healthy Ageing^{31,32,40} by using MASK (MACVIA-ARIA Sentinel Network). ARIA is developing a novel implementation strategy using mobile technology^{41,42} and a clinical decision support system⁴¹ that is deployed in 21 countries.⁴³ The ARIA 2016 revision will be embedded in the clinical decision support system for real-time patient stratification by using mobile technology.

Most of the recommendations are based on low- or very low-certainty evidence, mainly because of the imprecision of the estimated effects due to few patients being studied. For those questions, there is a need for more well-designed and executed randomized controlled trials that would measure and properly report all important outcomes.

Clinical implications: The 2016 revision of the ARIA guidelines offers updated advice for clinicians and patients about the most commonly used treatments for AR.

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