

Intermittent or permanent control in mild asthma – patient or doctor voices?

Control intermitent sau permanent în astmul ușor – vocea pacientului sau a medicului

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Abstract

The adherence to treatment of the patient with mild asthma suffers regardless of the type of action initiated by the doctor or the authorities. There is a patient's voice that is not always heard, and multiple causes of nonadherence can be due to the limits of current guidelines. In this article, I will review the nonadherence factors, the patients' motivations and their attempts to address their wishes by changing strategies for mild asthma that emphasize the interplay of intermittent treatment versus continued therapy, with the emergence of a new potential player in the antiasthma strategy: long-acting beta2-agonist and inhaled corticosteroid.

Keywords: adherence, mild asthma, intermittent therapy

Rezumat

Aderența la tratament a pacientului cu forme ușoare de astm are de suferit, indiferent de tipurile de acțiuni inițiate de medic sau de autorități. Există o voce a pacientului care nu este întotdeauna ascultată, iar cauzele multiple de neaderență pot fi alimentate și de limitele ghidurilor actuale. În acest articol, voi trece pe rând în revistă factorii de neaderență, motivațiile pacienților și încercările de a veni în întâmpinarea doleanțelor acestora prin schimbarea unor strategii în astmul ușor, care subliniază valențele tratamentului intermitent versus ale tratamentului continuu, cu apariția unui nou potențial jucător în strategia antiastmatică: beta2 adrenergic de lungă durată și corticosteroidul inhalator.

Cuvinte-cheie: aderență, astm ușor, tratament intermitent

All the doctors are dreaming to have a perfectly controlled asthma patient. This desideratum is difficult to achieve. If we look at the reasons, we realize there are many causes of nonadherence. Suboptimal or nonadherence to the treatment of asthma is associated with many health and economic burdens, and is particularly problematic in asthma and chronic obstructive pulmonary disease management, because of the heterogeneous patient populations, the variability of symptoms, comorbidities, device switching, disagreement on standardized definitions, and the need for an inhaled route for the drug administration⁽¹⁾.

Factors influencing adherence

Strategies to help ensure optimal adherence are discussed, including the choice of a patient-tailored inhaler, patient empowerment, education and training, and the potential of electronic monitoring and digital technology⁽¹⁾. There are multiple *intentional factors*, including ambivalence to (or lack of confidence in) treatment, diagnosis denial^(2,3), embarrassment about using inhalers in social situations, peer-group pressures (particularly applicable to adolescents), concerns about adverse events, and erroneous beliefs that the treatment can be stopped because symptoms have improved. There are other *unintentional factors* such as: poor inhaler technique (even though the patient thinks he or she is using it correctly), incorrect inhaler use, lack of understanding when to use an inhaler, forgetfulness and language barriers, the need for multiple devices and/or concomitant

conditions requiring polypharmacy, as well as a disruptive lifestyle (for example, frequent long-haul flights, shift work, and personal/family crises)^(4,5). Different authors identified many other problems bridging between intentional and nonintentional adherence, such as: *unintentional nonadherence due to sporadic forgetfulness* (e.g., caused by a busy lifestyle), *intelligent nonadherence*, which refers to intentional nonadherence as a result of a *reasoned decision to reject therapy* as described earlier, and *unwitting nonadherence*, which is a form of unintentional nonadherence, usually due to misunderstanding instructions or poor inhaler technique⁽⁶⁾.

Is this adherence different for different classes of medication?

Different authors found that 14-20% of the subjects with asthma who were prescribed controller medicines for the first time across all adherence measures did not fill their prescriptions and the mean proportion of days covered was 19% for inhaled corticosteroid (ICS), 30% for leukotriene antagonists (LTRA), and 25% for inhaled corticosteroid/long-acting β 2-agonists (ICS/LABA) over 12 months⁽⁷⁾. Long-term adherence to LTRAs and ICS/LABAs is better than to ICSs; however, among patients receiving a controller medication for the first time, primary adherence is better to ICSs than to LTRAs or ICS/LABAs⁽⁷⁾. Perrin and colleagues⁽⁸⁾ found that adherence to ICS/LABAs was better than to ICSs, and one potential reason was that the addition of a bronchodilator (LABA) provided the patient with immediate symptomatic ben-

efit and could therefore be taken more regularly compared with an ICS, which does not provide such an immediate benefit. It is plausible that adherence to ICS/LABAs was higher because those patients had more severe asthma and thus were more likely to need the ICS/LABAs⁽⁷⁾. There are three moments of nonadherence in relation to the therapy in asthma. For initiation, 28% of prescriptions issued to adults for new chronic disease medications were never dispensed and approximately one-quarter of patients prescribed new asthma therapy failed to collect their first prescription⁽⁹⁾. The reasons are: denial of diagnosis, disease awareness, lack of trust in healthcare professionals, medication fears, cognitive ability, affordability, and access to therapy^(10,11). For treatment implementation and persistence, the major barriers are: identifying correctly the controller inhalers (31% identified them incorrectly), using their controllers correctly (only 30% reported daily use of their controller inhalers)⁽¹²⁾, and poor inhaler technique (which ranged from 14% to 90%, with an average of 50%)⁽¹³⁾. In any case, higher levels of adherence were associated with a reduced risk of severe asthma exacerbations⁽¹⁴⁾.

Why the patient is not doing the right thing?

Usually, for the asthmatic patient, this disease is not very obvious in most cases, if we are thinking of the mild asthma. They use medication only when symptoms occur and avoid the treatment when it is perceived to be unnecessary⁽¹⁵⁾. When symptoms worsen, most patients simply increase their use of a short-acting β_2 -agonist (SABA), and are less likely to increase the use of their controller medication. This symptomatic treatment delays the initiation of effective controller treatment, and exacerbations follow^(16,17). Patient mistakes are fueled by patient or physician-related items. “Guides mistakes” are due to the recommendation in GINA of a SABA bronchodilator in step 1, which has no inherent antiinflammatory pharmacological properties, rather than an antiinflammatory medication such as an ICS⁽¹⁶⁾. SABA reinforces in the mind of patients the key and central role of SABA in asthma management⁽¹⁶⁾; the rapid relief of symptoms is another desire of mild asthma patient; SABA is feeding this hope of mild asthmatics – the great majority of patients are confident and willing to self-treat^(16,15) and SABA seems appropriate. The loss of autonomy, the addiction to regular treatment in step 2 and corticophobia reinforce the messages in favor of SABA. For many patients, the message that regular use of a SABA might be unsafe and even associated with asthma deaths^(16,18) is hard to grasp. LABA is contraindicated by guides as monotherapy, in comparison with SABA, accepted as standard, and it makes no difference even though there is evidence indicating that both SABA and LABA have serious risks as monotherapy^(19,20); there is no evidence to suggest that there is any difference in the risks associated with the regular “maintenance” use of either one. As recognized by O’Byrne et al.⁽¹⁶⁾, it’s a conflicting perception of need between patients and physicians, which might reinforce a patient’s false belief

that the asthma has been effectively controlled. The divergence in communication could be a factor in the overreliance on SABA and underuse of ICS. Patients perceived “well-controlled” as being able to manage their exacerbations with medical help or the use of medication, whereas only approximately 10% agreed with the physicians’ view that “asthma symptoms are nonexistent or minimal”⁽²¹⁾.

Looking for practical solutions is one of the alternatives

In years, a history was built, and it is possible to mark a change of the therapeutic behaviours of the doctors. A combination of step 1 and 2 in mild asthma can avoid the temptation of the patient to stop the ICS, from which no benefit is perceived, to revert to SABA use and to speculate the inclination towards SABA of these patients. The proposal of replacing SABA and ICS with a combination treatment comprising SABA or fast-acting LABA and ICS in a single inhaler, for as-needed use in patients with intermittent or infrequent symptoms, and increasing this to regular maintenance plus as-needed use in patients whose symptoms are persistent, is not new⁽¹⁶⁾. The as-needed use of an ICS/SABA or ICS/fast-acting LABA combination has been proposed as a potential treatment strategy for intermittent and mild asthma 13 years ago⁽²²⁾.

The first trial to see what happens in mild asthma using “on-demand therapy” versus “maintenance inhaled treatment” was made by Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute in 2005. Boushey and colleagues started modestly. The intermittent treatment with inhaled glucocorticoids based on of symptoms was as effective as the regular maintenance therapy with an inhaled glucocorticoid or a leukotriene receptor antagonist in maintaining peak expiratory flow and preventing exacerbations over a 12-month period, despite a much lower annual exposure to glucocorticoids with the as-needed therapy than with the maintenance therapy^(23,24). The disadvantage was the less improvement of asthma control scores and less symptoms-free days in the as-needed therapy versus regular treatment. In 2007, Papi et al.⁽²⁵⁾ conducted another trial and found that the as-needed use of a single inhaler containing albuterol and beclomethasone based on symptoms in mild and mild to moderate asthma was as effective as twice-daily beclomethasone, and it was associated with a much lower cumulative dose of glucocorticoid. In 2012, Calhoun et al., in the BASALT study, found no significant difference in the rate of treatment failure among patients with asthma who took an inhaled glucocorticoid only when they took as-needed albuterol, as compared with those who used inhaled glucocorticoids regularly⁽²⁶⁾. Two recent studies from 2018, starting from the fast effect of formoterol (Sygma 1 and Sygma 2), raised multiple questions for experts in case of mild asthma. Both studies included over 8000 patients with mild asthma^(27,28). These were double-blind trials, involving patients of 12 years of age or older, and the survey was

conducted for 52 weeks. In Sygma 1⁽²⁷⁾, the patients were randomly assigned to one of three regimens: twice daily placebo plus terbutaline (0.5 mg) used as-needed (terbutaline group), twice-daily placebo plus budesonide-formoterol (200 µg of budesonide and 6 µg of formoterol) used as-needed (budesonide-formoterol group), or twice-daily budesonide (200 µg) plus terbutaline used as-needed (budesonide maintenance group). The primary objective was to investigate the superiority of as-needed budesonide-formoterol to as-needed terbutaline with regard to electronically recorded weeks with well-controlled asthma. The first results demonstrated that in patients with mild asthma the as-needed budesonide-formoterol provided superior asthma symptom control compared to as-needed terbutaline, assessed according to the electronically recorded weeks with well-controlled asthma, but it was inferior to budesonide maintenance therapy; in the same time, the exacerbation rates with the two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide-formoterol used as needed resulted finally in a substantially lower glucocorticoid exposure than budesonide maintenance therapy. In Sygma 2⁽²⁸⁾, the patients were randomly assigned to receive twice-daily placebo plus budesonide-formoterol (200 µg of budesonide and 6 µg of formoterol) used as needed or budesonide maintenance therapy with twice-daily budesonide (200 µg) plus terbutaline (0.5 mg) used as needed. It was a more pragmatic study design, without daily reminders to use maintenance medication, to demonstrate that budesonide-formoterol used as needed would be non-inferior to regular budesonide maintenance treatment in preventing severe exacerbations in patients with mild asthma⁽²⁸⁾. The authors found interesting results: in mild asthma, budesonide-formoterol used as needed was non-inferior to twice-daily budesonide, with respect to the rate of severe asthma exacerbations during the 52 weeks of treatment, but was inferior in controlling symptoms. The patients in the budesonide-formoterol group had a clear advantage in an approximately one quarter of the inhaled glucocorticoid exposure compared to those in the budesonide maintenance group. The conclusions of both studies are interesting: the treatment with budesonide-formoterol on an as-needed basis prevented the most serious outcomes of poorly controlled asthma – exacerbations and loss of lung function – but it was less effective at mitigating symptoms⁽²⁵⁾. This effect appears at a median daily dose of inhaled glucocorticoid that was only 17%

to 25% of that in the regular maintenance group, reducing the side effects of inhaling corticoids and the costs.

Open questions remain after all these new reports:

- Are the doctors satisfied with this new concept of intermittent treatment, with good consequences, such as the prevention of exacerbations (main contributors to loss of lung function, death and cost)?
- Are all the patients happy enough with any symptoms or is there a need for rescue inhaler use?
- Is this new alternative treatment accepted finally by the guidelines and authorities, and it is improving real life of the capricious mild asthmatics patients? Of course, there are other possible strategies to improve the adherence of this type of asthmatic patients, such as⁽²⁹⁾:
 - personalised text messages sent by their phone⁽³⁰⁾ (an increase in adherence with 2.75% each month relative to no intervention);
 - dose simplification⁽³¹⁾, patient education⁽³²⁾, motivational interviewing⁽³³⁾, adherence feedback⁽³⁴⁾, provider communication skill training⁽³⁵⁾ and use of mobile communication technology⁽³⁶⁾;
 - collective interventions (most had a positive but modest impact on adherence)⁽²⁹⁾;
 - multifaceted interventions, that combined these strategies, were often more effective⁽³⁷⁾.

Conclusions

As B.G. Bender is advocating in one of his articles on adherence problems, “interventions are less or more prolific, but no silver bullet has arrived”⁽²⁹⁾. In the multitude of saving solutions offered by the experts to solve the adherence difficulties – such as improving medication delivery technology, “real world” studies closer to patients demands, and patient-centered care⁽²⁹⁾ –, we probably need in the future to take into account this new concept accepted easier by the mild asthmatic patients, with the combination of LABA/ICS as needed. There are now, especially for mild asthmatics, offers of ICS/formoterol or ICS/SABA combination products as reliever therapy instead of SABA monotherapy for patients in GINA steps 1 or 2. Of course, we need more studies, but this option would eliminate the problem of learned reliance and overreliance on SABA, and could eliminate the use of SABA-only products in asthma⁽¹⁶⁾. The concept must be “digested” by patients and doctors before entering in new guidelines. ■

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