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To cite this article: Luis J. Nannini (2019): Treat to target approach for asthma, Journal of Asthma, DOI: [10.1080/02770903.2019.1591443](https://doi.org/10.1080/02770903.2019.1591443)

To link to this article: <https://doi.org/10.1080/02770903.2019.1591443>



Published online: 23 Mar 2019.



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Treat to target approach for asthma

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ABSTRACT

Recognition that about half of asthma deaths might be preventable if recommended guidelines are followed suggests that better implementation of established management strategies is needed. However, to achieve a further substantive reduction in asthma mortality, novel strategies will also be required. It is well established that asthma is a disease of chronic inflammation, with episodes of worsening inflammation associated with increased symptoms and/or exacerbations; however, current guidelines paradoxically recommend that initial treatment is only symptomatic, rather than directed at the underlying inflammatory mechanism. The “Treat to target” (TTT) approach has become a popular concept in the medical management of several common chronic conditions, including rheumatoid arthritis (RA), diabetes, hypertension and hyperlipidemia. For example, as part of a TTT approach, rheumatologists recommend methotrexate for RA with onset within 6 months. Applying the TTT approach to asthma, the primary target could be clinical remission and the primary goals as follows: eliminate symptoms and exacerbation risk; prevent airway remodeling; and normalize lung function. To construct a TTT algorithm for chronic asthma, the proposal is to eradicate short-acting β_2 -agonists (SABA) at all asthma severity levels and replace SABA with “Anti-Inflammatory Reliever Therapy” (AIR), using inhaled corticosteroids (ICS)/SABA or ICS/formoterol. For individuals with equal to or less than 12 months’ history of symptoms, fewer than two symptoms per month, no exacerbations in the last 12 months and normal lung function, the recommendation is early initiation of ICS/SABA or ICS/formoterol as AIR.

Abbreviations: AIR: Anti-Inflammatory Reliever Therapy; DMAADs: disease modifying anti-asthmatic drugs; GINA: Global initiative for asthma; ICS: Inhaled corticosteroids; LABA: Long acting beta2 agonists; LAMA: Long acting muscarinic antagonists; PICO: population, intervention, comparator, and outcomes; PRN: pro re nata; RA: rheumatoid arthritis; SABA: Short acting beta2 agonists; TTT: Treat to target

ARTICLE HISTORY

Received 2 February 2019
Revised 28 February 2019
Accepted 3 March 2019

KEYWORDS

Asthma; asthma treatment; asthma guidelines; asthma pharmacology

Background

International trends in asthma mortality rates provide useful information about the burden of asthma and the impact of changes in asthma management [1].

Since the 1980s there has been a marked increase in the use of inhaled corticosteroids (ICS) in the management of asthma. This ICS-based management approach was associated with a widespread and progressive reduction in international asthma mortality of 63% over the 20-year period between 1985 and 2005 [2]. Since 2006, there has not been an appreciable change in global asthma mortality in 5–34-year olds [1]. In keeping with the asthma mortality surveys of the 1970s and 1980s, the characteristic circumstances associated with asthma mortality identified in a recent survey included over-reliance on and excessive use of β_2 -agonist drugs [3].

Most of individuals with asthma receive short-acting β_2 -agonist (SABA), with the potential of developing inappropriate patterns of use, which can interfere with ICS adherence [4]. Additionally, regular SABA use can lead to increased bronchial hyper-responsiveness, loss of asthma control, worsening lung function, and delays in seeking help [5–11]. In such circumstances, asthma might follow a progressive and detrimental disease course with an increased risk of life threatening exacerbations and respiratory arrest [4].

So while it is recognized that about half of asthma deaths might be preventable if recommended guidelines are followed, it is becoming increasingly clear that novel strategies will also be required to achieve further substantive reductions in asthma mortality [1].

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This manuscript is not under simultaneous consideration by any other publication.

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Main text

It is well established that asthma is a disease of chronic inflammation, with episodes of worsening inflammation associated with increased symptoms and/or exacerbations; however, current guidelines paradoxically recommend that initial treatment is only symptomatic, rather than directed at the underlying inflammatory mechanism [12]. Several studies confirm that when symptoms worsen, most patients simply increase their use of a SABA and are less likely to increase use of their controller medication. This symptomatic treatment delays the initiation of effective controller treatment and exacerbations follow [1,2,4]. GINA recommends as-required SABA alone at step one, which, unlike ICS, has no inherent anti-inflammatory pharmacological properties [13]. Despite this, there is robust evidence to recommend early intervention with ICS in asthma as follows:

1. Ongoing airway inflammation and airway remodelling has been observed in adolescents in clinical remission of atopic asthma [14,15].
2. Elevated exhaled nitric oxide levels and bronchial biopsy evidence of airway inflammation have been found in patients with mild, intermittent asthma [16].
3. Bronchoconstriction generates excessive mechanical forces within the airways that distort tissue cells [17]. This phenomenon might occur every time an individual with asthma uses SABA as needed.
4. Early initiation of low dose ICS leads to a greater improvement in lung function [18,19]. After 24 months of asthma symptoms budesonide 800 µg/day dose was needed to obtain similar improvement as 200 µg/day dose initiated within less than 12 months of asthma symptoms [20].

Two unresolved topics need to be faced in asthma management. First, poor controller therapy adherence and second the plateau in asthma mortality since 2006. One proposal to address these issues is to apply the “Treat to Target” (TTT) approach of the American College of Rheumatology Guideline for the treatment of rheumatoid arthritis (RA) [21] to asthma treatment and management. TTT has become an attractive concept in the clinical management of RA. TTT is generally defined as a treatment strategy in which the clinician treats the patient aggressively enough to reach and maintain explicitly specified and sequentially measured goals, such as remission or low disease activity [22]. TTT is proactive, has a clear

endpoint (the “target”), and can be operationalized as a specific treatment algorithm, simplifying the multitude of complex medication sequences that can be used to treat active RA. Treat to target has subsequently become a popular concept in the medical management of several other common chronic conditions, including diabetes, hypertension, and hyperlipidemia [22,23]. Shared decision making may be easier to implement in TTT strategies using specific targets as opposed to those requiring the use of specific medications, since the former enables physicians to incorporate their patients’ treatment preferences [24]. The primary target for treatment of RA should be a state of clinical remission. The primary goal of treating the patient with RA is to maximize long-term health-related quality of life through control of symptoms, prevention of structural damage, and normalization of function and social participation [22].

Applying the TTT approach to asthma, the primary target could also be clinical remission, and the primary goals eliminating symptoms and exacerbation risk, preventing airway remodeling and normalizing lung function.

To construct a TTT algorithm for chronic asthma the proposal includes eradicating short-acting β_2 -agonists (SABA) at all asthma severity levels and replacing SABA with “Anti-Inflammatory Reliever Therapy” (AIR), using inhaled corticosteroids (ICS)/SABA or ICS/formoterol [25–28]. For individuals with less than 12 months’ history of symptoms, fewer than two episodes of symptoms per month, no exacerbations in the last 12 months and normal lung function, the suggestion is early initiation of ICS/SABA or ICS/formoterol as AIR (Figure 1). For individuals with one or more features of more severe disease (i.e. more than two episodes of symptoms per month, one exacerbation in the prior 12 months or abnormal lung function) initiation of regular ICS (400 micrograms/day of inhaled budesonide or equivalent) is proposed as a disease modifying anti-asthmatic drug (DMAAD), analogous to monotherapy with methotrexate in early RA [21], plus ICS/formoterol as AIR. If an individual experiences an exacerbation, worsening symptoms or deteriorating lung function, the suggestion is to increase the dose of ICS/LABA plus AIR, then increase ICS dose, followed by the addition of a long-acting muscarinic antagonist (LAMA). Electronic monitoring of inhaler use will provide definitive adherence data before considering biologic therapy for those individuals whose asthma remains inadequately controlled.

The major differences between current GINA recommendations and the proposed algorithm are at the

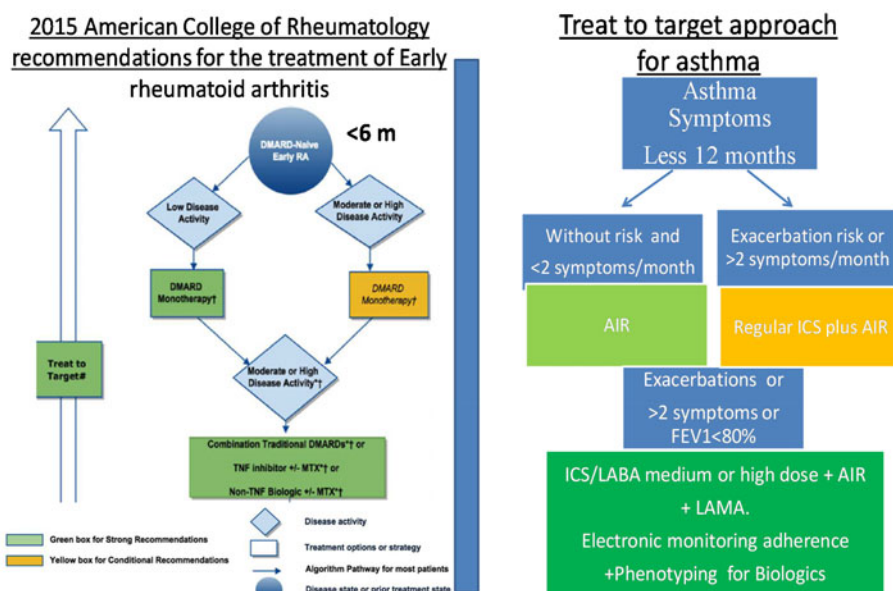


Figure 1. Treat to target approach for asthma, a parallelism with Rheumatoid arthritis recommendations (at the left), with permission from John Wiley and Sons [21]. AIR: Anti-Inflammatory Reliever Therapy; ICS/LABA: Inhaled Corticosteroids plus Long Acting Beta2 Agonists; LAMA: Long Anti-Muscarinic Antagonists. Formoterol is the only LABA with rapid onset of action like SABA. Electronic monitoring of inhaler use will provide definitive adherence before considering for biologic therapy.

two first steps. From moderate to refractory asthma the only one difference is the eradication of SABA and long-term oral corticosteroids [29]. Asthma recommendations and guidelines around the world consistently include SABA as an initial treatment option; but why? The reference for this management strategy in GINA is an anonymous review, so perhaps we use SABA mostly due to convention and habit [30]. The challenge is for guideline producers to break with tradition and consider an ambitious treat-to-target approach with a focus on achieving asthma remission even in mild, intermittent or recent onset asthma.

Conclusion

This proposed simplified asthma treatment algorithm aims to achieve asthma remission across all disease severities. The next step will be to establish key principles and PICO (population, intervention, comparator, and outcomes) development by an international organization in order to confirm its viability.

Acknowledgments

Rebecca Fortescue (née Normansell)|Joint Co-ordinating Editor, Cochrane Airways Population Health Research Institute St George's, University of London; because of editing and feedback for writing this manuscript.

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