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Managing asthma in the era of biological therapies

Philip G Bardin , David Price , Pascal Chanez , Marc Humbert , Arnaud Bourdin

Asthma treatments have been remarkably successful at controlling symptoms. Up to 75% of people with asthma can achieve adequate asthma control on inhaled corticosteroids (ICS) with or without long-acting β_2 -agonists (LABA).¹ But real-life studies have been sobering, indicating that full asthma control is only attained in about 30–40% of people with asthma.² Many patients retain impairment of lung function and poor quality of life.³

Suboptimal asthma control might occur for various reasons, but there is consensus that poor adherence with asthma medications is a cardinal cause.³ Studies have suggested that asthmatics are especially prone to lapse treatment during asymptomatic periods when having to take regular treatment interferes with their lifestyle. Patients also have concerns about long-term side-effects of ICS, and many choose to live with persistent asthma symptoms. Finally, since asthma is a disease characterised by chronic airway inflammation

with variable airflow limitation and unpredictable symptoms, treatment often requires frequent adjustment to achieve total control of chronic asthma. This aim might only be possible to attain in a small proportion of patients.

Improving adherence to asthma medication has proven difficult, despite educational strategies such as asthma management plans and simplified inhaler devices.³ For example, despite comprehensive educational asthma programmes targeting patients and general practitioners in countries like Australia, rates of adherence remain poor. There have also been schemes to educate patients about the long-term safety of ICS, but there remains considerable so-called corticophobia in the general population, and this is unlikely to change. Recognition of the key role of adherence has prompted novel approaches in other diseases. Introduction of directly-observed-therapy (DOT) in tuberculosis has resulted in improved

adherence with matching gains in cure rates.⁴ Whether this approach is applicable to asthma should perhaps be considered.

It can be argued that our current treatment paradigms for asthma are theoretical constructs that fail, at least in part, at a practical level. However, recent innovations might permit an alternative approach. First, asthma management has been improved by the implementation of maintenance and reliever therapy (MART) by use of an ICS-LABA combined inhaler. Patients are encouraged to use regular ICS and LABA but to augment inhaled treatment immediately when asthma symptoms flare. The strategy has been shown to reduce asthma exacerbations and lessen overall corticosteroid exposure.⁵ A recent non-industry funded, controlled study⁶ confirmed that MART had projected benefits on asthma exacerbations and corticosteroid exposure. MART has gradually gained acceptance worldwide as a feasible and working therapeutic option for asthma.⁷

A second important aspect is the successful development of biological drugs to optimally treat patients with severe asthma on the basis of disease phenotyping and biomarkers. Monoclonal antibody treatments such as anti-IgE, and more recently anti-IL-5, anti-IL-4, and anti-IL-13⁸ have shown their ability to treat so-called T2-related asthma. These studies have shown reductions in exacerbations and some improvements in lung function, asthma control, and quality-of-life outcomes. Most of the asthma population might be eligible for this kind of intervention. Importantly, these treatments can be administered at monthly intervals (or possibly longer) via subcutaneous injection and have minimal side-effects. They are therefore potentially suitable for strategies that implement DOT to improve adherence and disease control in asthma.

We therefore propose a new treatment paradigm for asthma. This approach has four steps (figure). First, people with asthma who are likely to respond to modulation of IgE, IL-5, IL-4, or IL-13 are identified. Second, daily ICS-LABA is replaced by biological therapy every month or every 2 months given as DOT. The patient's general practitioner can do this step and establish the optimal rhythm of injection. Third, patients are educated to use ICS-LABA or long-acting muscarinic-antagonists (LAMA) on an as-needed

basis (MART) for flares of asthma symptoms. Finally, patients are monitored to ensure asthma control is maintained.

Could this overhaul of current asthma approaches work? Several lines of evidence suggest that it might improve current practice. The use of MART strategies has gained wide acceptance and although DOT has chiefly been used in tuberculosis, it appears suitable for application in a chronic disease such as asthma. Biological therapies have been effective and several compounds have shown efficacy with a reasonable safety profile. Finally, an analogous therapeutic approach using pre-seasonal omalizumab injections in children has been successful.⁹

However, there are important caveats. Substantial clinical research will be required to examine the effectiveness and feasibility of the proposal. Strategies to combine randomised studies with real-life pragmatic studies, not only in severe asthma but also in mild asthma, will be essential. Studies will also be needed to validate the overall strategy; examine

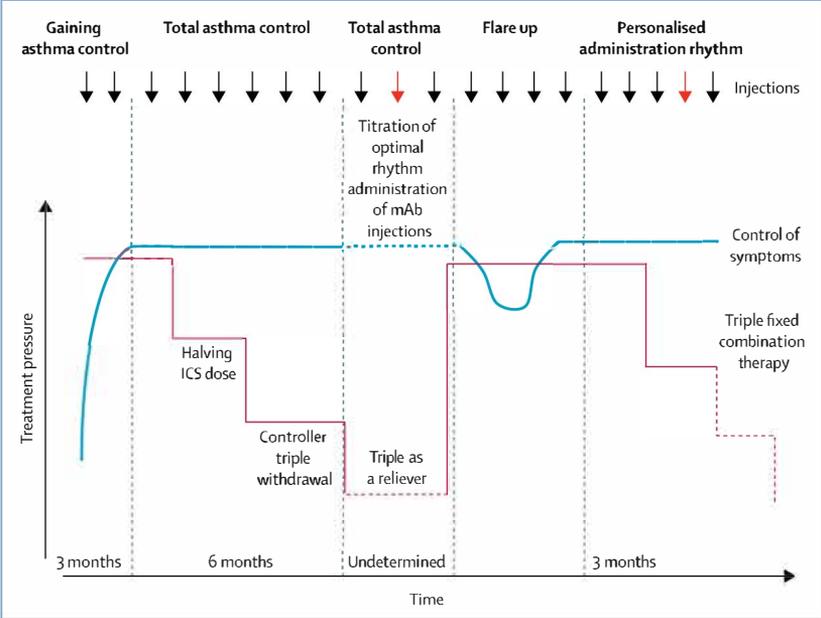


Figure: Proposed new asthma therapy scheme
 Arrows represent mAb injections; red arrows indicate accessory injections. The red line represents ICS dose within triple fixed combination therapy (supposing different ICS/LAMA/LABA combinations contain differing doses of ICS), and refers to the y axis, treatment pressure. During the total control phase, ICS dose is halved. Patients are then allowed to stop their regular, daily use of inhaled asthma medications ("triple", which means association of ICS, LABA and LAMA in the same device) once total asthma control is achieved thanks to the mAb injections (controller triple withdrawal). These inhalers will be kept only for treating flare up, as a symptom reliever, on demand. During the flare-up phase, the daily dose of ICS in inhaled therapies increases. For both the blue and red line, dashes indicate that the length of time in which asthma symptoms are totally controlled is undetermined. mAb=monoclonal antibody. ICS=inhaled corticosteroids. LABA=long-acting β 2-agonists. LAMA=long-acting muscarinic-antagonists.

asthma outcomes, costs, and viability; identify patients with a treatable trait who will benefit;¹⁰ and substantiate acceptability to populations with asthma.

The potential benefits of reversing asthma treatment paradigms are evident: improved adherence, enhanced asthma control, fewer side-effects from ICS-LABA medications, simplified asthma management and greater convenience for patients. Indeed, regular anti-inflammatory treatment with biological therapies has the potential to reduce overall asthma severity. Since safety concerns have been satisfactorily addressed, cost considerations are likely to be the major limitation to their use. If this issue can be mitigated a reversal of current treatment algorithms might have substantial benefits and improve asthma management.

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