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Modifying the trajectory of asthma—are there lessons from the use of biologics in rheumatology?

As we move towards a new era of precision medicine in high-income countries, with the conceptual framework of the right drug, for the right patient, and at the right time, it is useful to consider variations in the availability of targeted therapies for different diseases.

20 years ago rheumatology care involved treatment with oral disease-modifying drugs (DMARDs), oral corticosteroids, and analgesia with non-steroidal anti-inflammatory therapy to minimise disease progression and relieve symptoms. Physiotherapy and rehabilitation were also used in disease management. With the advent of biological DMARDs, there was a shift in disease management with initially improved symptoms and disease control in severe arthritis, followed by a treatment model aimed at disease remission.^{1,2} Now remission induction followed by drug tapering has emerged as a framework around which these treatments should be assessed.³ The bar has been raised for conventional synthetic DMARDs, forcing a rethink of goals so that treatment to a target of remission is now the accepted goal.⁴

As these new treatments became available, specialised rheumatology academic centres were established to optimise patient selection, management, and treatment

monitoring, and also to give trainees expertise in the prescription of these medications and subsequent monitoring. In time, as trainees moved from specialised centres into community-based settings, there was a greater comfort level within the rheumatology community in prescribing outside of the specialised centres. In keeping with this model, where specialised centres for the management of severe asthma have been established, improved outcomes have been shown and selective and appropriate use of biologics has occurred.⁵

Until fairly recently, asthma has lagged behind in the development of biologics, partly because of the efficacy of inhaled corticosteroids and, for more severe disease, their use in combination with long-acting β agonists with or without adjunct therapy, such as a leukotriene receptor antagonist or tiotropium bromide.⁶ Despite the use of these treatments, asthma remains uncontrolled in a proportion of patients at a considerable cost to the health-care system.⁷ The first biologic in asthma was omalizumab that targets IgE. Its efficacy is well documented in adults and children with atopic asthma for prevention of asthma exacerbations and improved symptom control and quality of life.⁸ A limitation of this therapy is the narrow therapeutic window for its efficacy

based on serum IgE concentrations.⁸ Although case series of its use in patients with higher than its regulatory approved IgE concentrations have been reported,⁹ this limitation remains a problem in severe asthma.

More recently, in parallel with the recognition that a minority of patients with asthma could not be controlled on first-line inhaled therapies,⁶ there has been an incremental understanding of the complex pathways underlying the biology of asthma. This increase in knowledge has led to the development of new potential targets for treatment. The therapy that is most advanced, mepolizumab, targets interleukin 5, a key inflammatory cytokine in asthma. The initial development of this class of drug was delayed because of the use of mepolizumab among a broad range of asthma patients.¹⁰ Subsequently, two investigator initiated trials^{11,12} showed mepolizumab to be effective in reducing asthma exacerbations in patients prone to exacerbations and with an increase in eosinophil concentrations although within the normal range. The evidence of efficacy has led to regulatory approval and commercial availability of this therapy.¹³ More recently, reslizumab has also received regulatory approval to treat patients with severe asthma.¹⁴ Benralizumab has shown similar efficacy¹⁵ and will probably be submitted for regulatory approval to the US Food and Drug Administration and European Medicines Agency later this year. With these new therapeutic options, and many other targeted therapies in late stage development,¹⁶ researchers need to explore whether these drugs might be used not as an end-stage treatment but at an earlier stage.

Unlike the early stages of the use of biologics in rheumatology, there is an emerging framework for the use of biologics in asthma that will allow for the appropriate targeting of treatment to specific patients. This refinement in descriptors of patients with asthma will require a new taxonomy for asthma such that patients with a history of asthma exacerbations and with well defined cut points in peripheral eosinophil blood concentrations could be labelled as interleukin-5 responders.¹³ Similar patient profiles for potential responsiveness to anti-interleukin 4 and anti-interleukin 13 have been postulated.¹⁷

Omalizumab might be informative in that it is being assessed in a phase 3 randomised controlled trial in infants at high risk of asthma to explore its efficacy in preventing the development of asthma.¹⁸ However, it is speculative at

this stage to suggest that these newer biologics may have the capacity to be introduced at an earlier disease stage and modify the course of asthma. Yet, as understanding of their role in more severe asthma advances, future research might address this notion of their earlier use. Evaluation of the potential efficacy of such interventions will require careful cost-effectiveness studies and, ultimately, real world efficacy trials. Such assessments will require use of robust disease models that project not only potential benefits of these drugs but also their associated costs.¹⁹

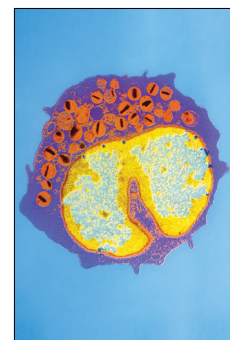
Greater awareness of the underlying biology of asthma has provided a new range of treatments, especially for more severe uncontrolled asthma. In rheumatology, biologics were initially introduced for more severe end-stage disease but then were integrated at an earlier stage in disease presentation to modify progression. Conceptually, researchers can learn from this experience to inform research on the optimum framework for evaluating the future role for biologics in asthma.

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JMF has been involved in the evaluation of treatment strategies for more severe asthma as discussed in this Comment. He has received research funding, including for biologics being evaluated to treat severe asthma, paid directly to the University of British Columbia, from AstraZeneca and GlaxoSmithKline; has received speakers' fees for participating at symposia on severe asthma and biologics funded by AstraZeneca; and has participated in the protocol development of studies funded by AstraZeneca evaluating biologics in severe asthma. PE has had no involvement in the development of biologics for asthma; he has undertaken clinical trials funded by, and provided expert advice for, Pfizer, MSD, AbbVie, Bristol-Myers Squibb, UCB, Roche, Novartis, Samsung, and Lilly.

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Beyond health: five global policy metaphors for civil registration and vital statistics

Panel: Five global policy metaphors for CRVS

CRVS as public health

CRVS maximises good health and wellbeing. CRVS data provide the evidence base for government policy decision making on population health and intersectoral issues connected to the social determinants of health. CRVS data are needed for mortality surveillance and research. Birth certification enables populations to access medical services and public health insurance and facilitates universal health coverage.

CRVS as sustainable development

CRVS promotes key pillars of human development, including equity, participation in economic, social, and political life, empowerment, security, and sustainability. CRVS data are used across multiple sectors and support country, regional, and global development policy, planning, implementation, and monitoring, including of the SDGs.

CRVS as investment

CRVS maximises countries' economic planning and development. CRVS data allow governments and their partners to develop cost-effective policies and interventions that improve population health. Governments can use CRVS to improve financial management, resource allocation, transparency, and accountability, and their country's overall macroeconomic landscape.

CRVS as human rights

CRVS maximises access to human rights entitlements, especially for vulnerable and marginalised populations, and women and girls. CRVS facilitates recognition of the right to identity, name, and nationality and associated rights. For children, CRVS can protect against child labour, child marriage, and trafficking. CRVS as human rights overlaps with the SDG aspiration that "no one shall be left behind", something that cannot be achieved if all people are not recognised and counted.

CRVS as good governance

CRVS maximises government accountability. A strong legislative framework associated with CRVS, and the ability of the state to know its population, enables good governance, transparency, and accountability.

CRVS=civil registration and vital statistics. SDGs=Sustainable Development Goals

Civil registration and vital statistics (CRVS) systems and the data they generate will be crucial for monitoring implementation of the Sustainable Development Goals (SDGs) in countries, as well as for other national and regional health and development agendas.¹ It is the continuity, completeness, and relevance at local administrative levels that distinguish CRVS information from other population data sources. In 2015, the *Lancet* Counting Births and Deaths Series² responded to an earlier *Lancet* Series, *Who Counts?*³ that described the neglect of global CRVS systems as "the single most critical failure of development over the past 30 years". Notably, the 2015 Series showed how CRVS systems are an essential component for global achievement of the Millennium Development Goals.^{2,4–6} Although global health commentators typically focus on CRVS systems to support global health policy goals,⁷ improving national CRVS systems can be justified for reasons beyond health.

Adapting David Stuckler and Martin McKee's five metaphors on global health,⁸ we identify five global policy metaphors that underline the centrality of CRVS systems for development: CRVS as public health, sustainable development, investment, human rights, and good governance (panel). With policy decision-making processes difficult to define, and subject to sensitive in-country trade-offs unrelated to the health portfolio, securing support for CRVS can "crucially depend on which metaphor is dominant".⁸