

The Chinese public health system needs to act on the worrying increase in adolescents smoking. Other health-related issues among adolescents such as obesity and myopia have already been addressed at the highest level. For instance, in August, 2018, President Xi Jinping committed to addressing the high incidence of myopia in Chinese children;¹⁰ smoking among adolescents is a problem that is at least as important. There are few tasks that are more urgent for public health in China than keeping adolescents away from tobacco.

Dan Xiao, *Chen Wang

Tobacco Medicine and Tobacco Cessation Center (DX) and Department of Pulmonary and Critical Care Medicine (CW), Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China; WHO Collaborating Center for Tobacco Cessation and Respiratory Diseases Prevention, Beijing, China (DX, CW); National Clinical Research Center for Respiratory Diseases, Beijing, China (DX, CW); Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100029, China (DX, CW); and Department of Respiratory Medicine, Capital Medical University, Beijing, China (DX, CW)
wangchen@pumc.edu.cn

We declare no competing interests.

- 1 Ministry of Health. China Report on the health hazards of smoking. Beijing: People's Medical Publishing House, 2012.
- 2 Wang M, Luo X, Xu S, et al. Trends in smoking prevalence and implication for chronic diseases in China: serial national cross-sectional surveys from 2003 to 2013. *Lancet Respir Med* 2019; 7: 35–45.
- 3 National Health Commission of the People's Republic of China. Regulation on smoking control in public places. <http://www.nhfpc.gov.cn/xcs/s3582/201411/cc090d9b0be641ac942daf1b101982b4.shtml> (accessed Nov 28, 2018; in Chinese).
- 4 National Health Commission of the People's Republic of China. Institutional functions. <http://www.nhfpc.gov.cn/zhuz/jgzn/lmtt.shtml> (accessed Nov 20, 2018).
- 5 Pan J, Han W. Exploring the intergenerational persistence of health behaviour: an empirical study of smoking from China. *BMC Public Health* 2017; 17: 557.
- 6 Loureiro ML, Sanz-de-Galdeano A, Vuri D. Smoking habits: like father, like son, like mother, like daughter. *Oxf Bull Econ Stat* 2010; 72: 717–43.
- 7 WHO. Parties to the WHO Framework Convention on Tobacco Control. http://www.who.int/fctc/signatories_parties/en (accessed Nov 26, 2018).
- 8 China Tobacco Market. Production and operation scheduling meeting of National Bureau of China Tobacco Company. http://www.etmoc.com/gedi/gedilist.asp?news_id=107018 (accessed Nov 20, 2018).
- 9 Xiao D, Bai CX, Chen ZM, et al. Implementation of the World Health Organization Framework Convention on Tobacco Control in China: an arduous and long-term task. *Cancer* 2015; 121 (suppl 17): 3061–68.
- 10 Xinhua News Agency. Take care of children's eyes and let them have a bright future. http://www.xinhuanet.com/politics/2018-08/28/c_1123341203.htm (accessed Nov 26, 2018; in Chinese).

2-year safety and efficacy results for benralizumab

The era of biological therapies for asthma started with approval in 2003 of a humanised anti-IgE antibody, omalizumab, for the treatment of patients with severe allergic asthma. Since then, IgG antibodies targeting interleukin (IL)-5 (mepolizumab and reslizumab) and IL-5 receptor α (benralizumab) have been approved for the treatment of patients with severe eosinophilic asthma characterised by recurrent exacerbations. In 2016, two phase 3 studies^{1,2} showed that benralizumab had good safety and efficacy when administered over 1 year in patients with severe uncontrolled asthma, reducing asthma exacerbations and improving lung function in patients with blood eosinophil counts of 300 cells per μ L or greater at baseline. Although 1-year safety results for anti-IL-5 or anti-IL-5 receptor α antibodies have generally been acceptable,³ no study has assessed their long-term safety or efficacy.

In *The Lancet Respiratory Medicine*, William W Busse and colleagues⁴ report the results of BORA, a 1-year extension study of two phase 3 trials (SIROCCO and CALIMA)^{1,2} in about 2000 adult (≥ 18 years) and

adolescent (12–17 years) patients with severe, uncontrolled eosinophilic asthma. In BORA, patients who were on placebo in the SIROCCO or CALIMA trials were randomly reassigned to receive subcutaneous benralizumab 30 mg either every 4 weeks (Q4W) or every 8 weeks (Q8W), whereas individuals on benralizumab Q4W or Q8W in those trials continued to receive their existing treatment regimens.

The proportion of patients with adverse events in BORA, including serious adverse events and those leading to treatment discontinuation, was similar to the proportions of patients with adverse events in the benralizumab treatment groups in SIROCCO or CALIMA. In the group treated with benralizumab Q8W (the approved treatment regimen in many countries) for 2 years in BORA, only eight (2%) of 512 patients discontinued treatment because of an adverse event. These observations over 2 years are reassuring, confirming the 1-year findings of no excess in viral or bacterial infections or hypersensitivity adverse events (eg, anaphylactic reactions or urticaria). No patient had a parasitic infection, which is surprising considering



Darren Hayes/Icon Images/Science Photo Library

Published Online
November 8, 2018
[http://dx.doi.org/10.1016/S2213-2600\(18\)30468-5](http://dx.doi.org/10.1016/S2213-2600(18)30468-5)
See [Articles](#) page 46

the important role of eosinophils in protecting against these infections and that benralizumab reduced and maintained blood eosinophil counts at almost zero.

The proportion of patients with anti-drug antibodies was similar after 1 year (13%) and 2 years (11%) of treatment with benralizumab Q8W, although these were higher than reported after 1 year of treatment with subcutaneous mepolizumab (8%) or intravenous reslizumab (5%).⁵ The presence of anti-drug antibodies was not associated with reduced treatment efficacy in BORA, although the authors noted a slight decrease in eosinophil-depleting activity due to high anti-drug antibody titres at very low trough concentrations of benralizumab.

12 (1%) of 1576 patients in BORA had independently adjudicated new malignancies, of which only one (prostate cancer in a patient who remained on benralizumab Q8W from the previous study) was considered to be related to the study drug. However, a longer period of observation will be needed to completely exclude any potential link with cancer, as has been done for omalizumab.⁶

In terms of efficacy, the beneficial effects of benralizumab, including reduced exacerbations and improved lung function, asthma control, and quality of life, were maintained into the second year of treatment. The therapeutic response in those switching to benralizumab from placebo was similar to that in those who were already on benralizumab from the preceding studies. One interesting question is whether there could be an accrual benefit of benralizumab. This hypothesis is supported by the fact that, for patients in the benralizumab Q8W group with blood eosinophil counts of 300 cells per μL or greater at baseline, the annual rate of exacerbations was lower after 2 years (0.46 [95% CI 0.39–0.53]) than after 1 year (0.57 [0.47–0.68]). However, without a control group for comparison, this potential accrual of benefit cannot be entirely confirmed. Neither was it possible to ascertain whether those with a blood eosinophil count of less than 300 cells per μL at baseline continued not responding, or responded less well, to benralizumab than did those with a blood eosinophil count of 300 cells per μL or greater at baseline, as previously shown in the SIROCCO and CALIMA trials. Finally, it is not clear whether there was any evidence of disease modification. The fact

that blood eosinophil counts increased towards pre-treatment levels 12 weeks after discontinuation of benralizumab in adult patients, with worsening of asthma control and quality of life, suggests that the drug is not able to modify the disease over a 2-year period. Longer follow-up is needed to assess this effect of the drug.

This 2-year follow-up of benralizumab therapy has provided reassuring data on its long-term safety and efficacy in patients with severe, uncontrolled eosinophilic asthma. However, it is essential that long-term follow-up continues to monitor safety issues, confirm efficacy, and explore the issue of disease modification. Given that benralizumab depletes eosinophils through a cytolytic process, whereas reslizumab and mepolizumab impede terminal differentiation of eosinophil precursor cells by blocking the effects of IL-5 in bone marrow, it would be advisable to provide long-term follow-up data for these drugs too. This new era of biological therapies promises to provide much needed effective treatments for a group of patients in whom standard therapies have failed.

Kian Fan Chung

National Heart & Lung Institute, Faculty of Medicine, Imperial College London, London SW3 6LY, UK; and Respiratory Unit, Royal Brompton & Harefield NHS Foundation Trust, London, UK
f.chung@imperial.ac.uk

I declare receiving honoraria for participating in advisory board meetings of GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Teva, Novartis, and Merck regarding treatments for asthma and chronic obstructive pulmonary disease and remuneration for speaking engagements.

- 1 Bleeker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016; **388**: 2115–27.
- 2 FitzGerald JM, Bleeker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016; **388**: 2128–41.
- 3 He LL, Zhang L, Jiang L, Xu F, Fei DS. Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: a pairwise and Bayesian network meta-analysis. *Int Immunopharmacol* 2018; **64**: 223–31.
- 4 Busse WW, Bleeker ER, FitzGerald JM, et al. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med* 2019; **7**: 46–59.
- 5 Matucci A, Vultaggio A, Danesi R. The use of intravenous versus subcutaneous monoclonal antibodies in the treatment of severe asthma: a review. *Respir Res* 2018; **19**: 154.
- 6 Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol* 2014; **134**: 560–67.