

Dex Pramipexole: A Potential Non-biologic Alternative for Patients with Eosinophilic Asthma?

Fei Li Kuang

Northwestern University Feinberg School of Medicine, Division of Allergy and Immunology, Chicago, IL, USA

DOI: <https://doi.org/10.17925/USRPD.2022.7.2.36>

Dex Pramipexole offers a potential non-biologic option for patients with eosinophilic asthma in that it lowers blood eosinophil count and improves lung function parameters. However, longer-term studies in patients treated by reducing blood or tissue eosinophils, whether through biologics or oral therapies, are needed to better understand the role of the eosinophil in human biology and disease pathogenesis and to better delineate the clinical efficacy of Dex Pramipexole in asthma.

Keywords

Asthma, biologics, dex Pramipexole, eosinophilic asthma, eosinophils, pre-biologic

Disclosure: Fei Li Kuang receives research funding from AstraZeneca to study the predictors of response to benralizumab treatment in hypereosinophilic syndrome within a phase III clinical trial.

Review process: Double-blind peer review.

Compliance with ethics: This article is an opinion piece and does not report on new clinical data, or any studies with human or animal subjects performed by the author.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this study.

Authorship: The named author meets the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and has given final approval for the version to be published.

Access: This article is freely accessible at touchRESPIRATORY.com © Touch Medical Media 2022

Received: 8 August 2022

Accepted: 18 October 2022

Published online: 18 November 2022

Citation: *touchREVIEWS in Respiratory & Pulmonary Diseases*. 2022;7(2):36–7

Corresponding author: Fei Li Kuang, Northwestern University Feinberg School of Medicine, Division of Allergy and Immunology, 240 E Huron St, Chicago, IL 60611, USA. E: feili.kuang@northwestern.edu

Support: No funding was received in the publication of this article

There is a wide range of eosinophil-associated disorders, from common conditions, such as eosinophilic asthma and chronic rhinosinusitis with nasal polyps (CRSwNP), to rarer ones, such as eosinophilic gastrointestinal disorders and hypereosinophilic syndrome (HES). The advent of eosinophil-targeted therapies is uncovering which of these disorders are primarily treatable by reducing blood or tissue eosinophils, thus giving us an insight into the underlying mechanisms of these diseases.

Dex Pramipexole is an enantiomer of the dopamine agonist Pramipexole that was approved by the US Food and Drug Administration in January 1997. It is used to treat Parkinson's disease and restless leg syndrome.¹ Dex Pramipexole was originally investigated to treat amyotrophic lateral sclerosis (ALS).² However, the phase III of the original clinical study was halted when dex Pramipexole did not show efficacy in treating ALS (Phase 3 study of dex Pramipexole in ALS [EMPOWER]; ClinicalTrials.gov identifier: NCT01281189).³ Dex Pramipexole was applied to the treatment of eosinophilic disorders when it was noted that patients in the original ALS trials demonstrated a reduction in blood eosinophil count over 3 months.⁴

A phase II, proof-of-concept study in 10 patients with HES showed that a dex Pramipexole treatment of 150 mg orally twice a day resulted in both haematologic and symptomatic improvements after 12 weeks in corticosteroid-sensitive patients (Study to evaluate safety and efficacy of dex Pramipexole [KNS-760704] in subjects with HES; ClinicalTrials.gov identifier: NCT02101138).⁵ One noteworthy benefit of this small study was that it highlighted dex Pramipexole as the first oral non-corticosteroid to show a complete reduction of tissue eosinophils in subjects with eosinophilic gastrointestinal disorder (n=2), and this reduction was associated with symptom improvement.⁵ However, the study was limited by its sample size (N=10) and the lack of objective measures for clinical symptom improvement, which is common when studying eosinophilic disorders with a wide range of clinical manifestations such as HES.^{5,6}

When applied to patients with CRSwNP (N=16), an open-label study of dex Pramipexole treatment resulted in significant blood and nasal polyp tissue eosinophil reduction, with the geometric mean absolute eosinophil count (AEC) dropping from 525 cells/ μ l to 31 cells/ μ l ($p<0.001$) and the tissue eosinophils reducing from a mean of 168 cells to 5 cells per high-power field ($p=0.001$) after 6 months.⁷ However, there was no change in total polyp size and, importantly, no significant change in patient nasal symptoms.⁷ These two small initial studies in patients with HES and CRSwNP indicated that dex Pramipexole could lower both blood and tissue eosinophils and that it was associated with symptomatic improvement in some eosinophilic disorders and perhaps not others.^{5,7}

The EXHALE trial is a double-blind, placebo-controlled, dose-finding phase II study of dex Pramipexole in adult patients with moderate-severe eosinophilic asthma (Dex Pramipexole dose-ranging biomarker study in subjects with eosinophilic asthma [AS201]; ClinicalTrials.gov identifier: NCT04046939).⁸ These subjects were already on steps 3 to 5 of asthma therapy, which include daily inhaled corticosteroids and long-acting beta-agonist combinations. Additional inclusion criteria included a pre-bronchodilator forced expiratory volume in 1 second (pre-BD FEV1) of $<80\%$ but $\geq 40\%$, with

reversibility in respiratory obstruction (≥ 200 mL, $\geq 12\%$), AEC ≥ 300 cells/ μ l at screening and an asthma control questionnaire (ACQ) score of ≥ 1.5 . Four groups of 25–28 subjects were formed according to the following doses: dex Pramipexole at 300 mg/day, 150 mg/day, 75 mg/day and placebo. The study met its primary endpoint (change in AEC from baseline), showing a statistically significant reduction in AEC after 12 weeks of therapy compared with placebo and in a dose-dependent manner (75 mg/day: $p=0.0190$; 150 mg/day: $p=0.0014$; 300 mg/day: $p<0.0001$). The secondary endpoints, which included measuring pre-BD FEV1 at 12 weeks, were also improved over placebo (75 mg/day: $p=0.0198$; 150 mg/day: $p=0.1337$; 300 mg/day: $p=0.0309$). In particular, the change in pre-BD FEV1 appeared to be more profound in those who had the greatest reduction in AEC at week 12 ($\geq 50\%$: $p=0.0036$).⁸

The improvements in a composite score that included both forced vital capacity and pre-BD FEV1 led the EXHALE authors to suggest that dex Pramipexole has an effect on mucus plugging.⁹ The study reports that measurements of nasal eosinophil peroxidase (EPX), an eosinophil granule protein, are decreased in the treatment group.⁹ Since nasal EPX has been described as a surrogate marker for sputum or lower airway eosinophilia, the study suggests that dex Pramipexole decreases sputum or lower airway eosinophilia, without a direct measure of sputum eosinophils. Taken together, these data suggest that dex Pramipexole is effective in lowering blood eosinophil count, improving spirometry parameters and affecting tissue eosinophils in the form of nasal secretions of EPX in adult patients with eosinophilic asthma.^{8,9}

Currently, the only published data on the use of dex Pramipexole in patients with asthma are in the form of abstracts presented at conferences.^{8–10} While patient symptom scores (ACQ) were collected at baseline in the EXHALE study, it is unclear if patients experienced fewer flares, as they did not exhibit lower ACQ scores with dex Pramipexole treatment than with the placebo.¹⁰ In addition, other asthma studies of biologics enrolled patients who experienced asthma flares within the past year despite being on maintenance therapy.¹¹ Larger, phase III studies will need to enrol similar patients and examine the effect of dex Pramipexole on clinical outcomes in asthma to compare it with the findings of trials on asthma biologics.

The mechanism of action for dex Pramipexole in regulating eosinophilia is unknown. A 1979 study found that high doses of L-dopa given centrally result in circulating eosinopenia in rats, suggesting that central dopamine agonism may regulate blood eosinophils.¹² Dopamine receptors D3 and D5 expression was detected on $<5\%$ of eosinophils in one study,¹³ but these are not mentioned in recent reviews. In the phase II, open-label

HES trial (ClinicalTrials.gov identifier: NCT02101138), bone marrow biopsies were performed at baseline and at week 12 and showed that drug treatment resulted in a selective absence of mature eosinophils.⁵ Unlike eosinophil biologics and corticosteroids, which act fairly quickly, dex Pramipexole appears to require several months before eosinophil levels in the blood reach their nadir. This suggests, though it is not proof, that the drug acts at the level of eosinopoiesis rather than by causing cell death. Indeed, the drug target might not even be the eosinophil cell itself but perhaps a surrounding epithelial cell or bone marrow stromal cell with an eosinophil-specific role.

If found to be effective in treating asthma, dex Pramipexole could be an alternative or add-on therapy to biologics, especially eosinophil-specific ones. While it would likely be more cost-effective compared with biologics, there are some practical drawbacks to dex Pramipexole, such as requiring a longer time to demonstrate haematological efficacy and twice-a-day dosing, which can be challenging even for adults compared with injections once every 2 months (benralizumab), every month (mepolizumab, reslizumab and tezepelumab) or every 2 weeks (dupilumab and omalizumab). Dex Pramipexole could be compared with another oral therapy for asthma, the leukotriene receptor antagonist montelukast, often chosen for its additional effect on allergic rhinitis and, in the paediatric population, for its ease of use and lack of corticosteroid.^{14,15} Head-to-head trials with montelukast or similar leukotriene modifiers may help identify whether dex Pramipexole is more effective or is effective for a subset of patients for whom leukotriene modifiers are insufficient. Finally, as with all eosinophil-targeted therapies, not much is known about the long-term effect of eosinophil reduction and depletion in humans, though short-term studies and case reports suggest the effect to be less severe than the one that is predicted by murine studies.^{16–18} In select groups of adult asthma patients who chose to continue on anti-interleukin-5 or anti-interleukin-5R α biologics after the completion of the original clinical trials (reviewed in Kuang and Bochner¹⁶, and Korn et al.¹⁹), there do not appear to be safety concerns after up to 5 years of treatment.^{16,19} However, it is noteworthy that these groups exclude people with a recent malignancy within 1 year, parasitic disease within 6 months and other significant medical conditions of concern to the investigators, as well as those who are pregnant.^{16,19}

Taken together, these studies present dex Pramipexole as a potential non-biologic option for patients with eosinophilic asthma, given its blood eosinophil-lowering effect and the improvement in lung function parameters. Larger studies are needed to better delineate its clinical efficacy in asthma and its safety profile in long-term use. \square

1. U.S. Food and Drug Administration. PRAMIPEXOLE DIHYDROCHLORIDE approval. 1997. Available at: www.accessdata.fda.gov/drugsatfda_docs/nda/98/020667a_applr.pdf (accessed 2 November 2022).
2. Cudkovic M, Bozik ME, Ingersoll EW, et al. The effects of dex Pramipexole (KNS-760704) in individuals with amyotrophic lateral sclerosis. *Nat Med*. 2011;17:1652–6.
3. Cudkovic ME, van den Berg LH, Shefner JM, et al. Dex Pramipexole versus placebo for patients with amyotrophic lateral sclerosis (EMPOWER): A randomised, double-blind, phase 3 trial. *Lancet Neurol*. 2013;12:1059–67.
4. Dworetzky SI, Hebrank GT, Archibald DG, et al. The targeted eosinophil-lowering effects of dex Pramipexole in clinical studies. *Blood Cells Mol Dis*. 2017;63:62–5.
5. Panch SR, Bozik ME, Brown T, et al. Dex Pramipexole as an oral steroid-sparing agent in hypereosinophilic syndrome. *Blood*. 2018;132:501–9.
6. Kovacs N, Benjamin K, Holland-Thomas N, et al. Symptom assessment in hypereosinophilic syndrome: Toward development of a patient-reported outcomes tool. *J Allergy Clin Immunol Pract*. 2020;8:3209–12.e8.
7. Laidlaw TM, Prussin C, Panettieri RA, et al. Dex Pramipexole depletes blood and tissue eosinophils in nasal polyps with no change in polyp size. *Laryngoscope*. 2019;129:E61–6.
8. Prussin C, Panettieri RA, Bozik ME, et al. Oral dex Pramipexole efficacy in lowering blood eosinophils in patients with moderate to severe uncontrolled eosinophilic asthma. Presented at: American Thoracic Society International Conference, Virtual Poster presentation, 17 May 2021. Abstract A1359.
9. Prussin C, Bozik ME, Mather JL, et al. The oral eosinophil-lowering drug dex Pramipexole improves FEV1 largely through its effect on FVC. Presented at: American Academy of Allergy Asthma and Immunology Annual Meeting, Phoenix, 28 February 2022. Poster #052.
10. Siddiqui S. Phase 2 trial evaluating the effect of dex Pramipexole on eosinophil biomarkers and lung function in asthma. Presented at: ERS International Congress 2021, Virtual, 8 September 2021.
11. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): A multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651–9.
12. Podolec Z, Vetulani J, Bednarczyk B, Szczeklik A. Central dopamine receptors regulate blood eosinophilia in the rat. *Allergy*. 1979;34:103–10.
13. McKenna F, McLaughlin PJ, Lewis BJ, et al. Dopamine receptor expression on human T- and B-lymphocytes, monocytes, neutrophils, eosinophils and NK cells: A flow cytometric study. *J Neuroimmunol*. 2002;132:34–40.
14. Nayak A, Langdon RB. Montelukast in the treatment of allergic rhinitis: An evidence-based review. *Drugs*. 2007;67:887–901.
15. Blake KV. Montelukast: Data from clinical trials in the management of asthma. *Ann Pharmacother*. 1999;33:1299–314.
16. Kuang FL, Bochner BS. Lessons learned from targeting eosinophils in human disease. *Semin Immunopathol*. 2021;43:459–75.
17. Kuang FL, Fay MP, Ware J, Wetzler L, et al. Long-term clinical outcomes of high-dose mepolizumab treatment for hypereosinophilic syndrome. *J Allergy Clin Immunol Pract*. 2018;6:1518–27.e5.
18. Manetz S, Maric I, Brown T, et al. Successful pregnancy in the setting of eosinophil depletion by benralizumab. *J Allergy Clin Immunol Pract*. 2021;9:1405–7.e3.
19. Korn S, Bourdin A, Chupp G, et al. Integrated safety and efficacy among patients receiving benralizumab for up to 5 years. *J Allergy Clin Immunol Pract*. 2021;9:4381–92.e4.