Safety of tiotropium Respimat (R) in black or African-American patients with symptomatic asthma

Graham, LeRoy M; Kerstjens, Huib A M; Vogelberg, Christian; Hamelmann, Eckard; Szefler, Stanley J; Pisternick-Ruf, Wendelgard; Engel, Michael; El Azzi, Georges; Unseld, Anna; Foggs, Michael B

Published in:
Respiratory Medicine

DOI:
10.1016/j.rmed.2019.07.002

Publication date:
2019

Respiratory Medicine 155 (2019) 58–60

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Short communication

Safety of tiotropium Respimat® in black or African-American patients with symptomatic asthma

LeRoy M. Graham[a,*], Huib A.M. Kerstjens[b], Christian Vogelberg[c], Eckard Hamelmann[d], Stanley J. Szefler[e], Wendelgard Pisternick-Ruf[f], Michael Engel[g], Georges El Azzi[g,1], Anna Unseld[f], Michael B. Foggs[h]

[a] Mercy Care of Atlanta, City of Refuge Clinic, Atlanta, Georgia, USA
[b] University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[c] University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany
[d] Evangelisches Klinikum Bethel gGmbH, Bielefeld, Germany
[e] The Breathing Institute, Children's Hospital Colorado, Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA
[f] Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Germany
[g] Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany
[h] Advocate Health Care, Chicago, IL, USA

ARTICLE INFO

Keywords:
Asthma
Black or african american
Adult
Pediatric
Tiotropium
Safety

ABSTRACT

Background: Black patients with asthma have a higher disease burden and greater morbidity compared with other racial/ethnic groups. Tiotropium Respimat®, as add-on to at least inhaled corticosteroids (ICS), improves lung function and asthma control and reduces asthma exacerbation risk in patients, with a safety profile comparable with placebo. This study aimed to assess the safety of tiotropium Respimat®, compared with placebo, in black or African-American patients.

Methods: Data were pooled from 12 randomized, placebo-controlled, parallel-group, Phase II or III trials from the global Boehringer Ingelheim program with once-daily tiotropium Respimat® (5 µg or 2.5 µg). Trial participants had symptomatic persistent asthma with a broad range of severities and were aged 1–75 years. The safety results of black or African-American patients were compared with the overall trial population.

Results: Of the 5165 patients treated with tiotropium or placebo, 3.2% were black or African American. For both doses of tiotropium, the proportion of patients reporting adverse events (AEs) was approximately 10% lower compared with placebo and was generally comparable with the proportion of patients reporting AEs in all groups of the overall population. The number of investigator-assessed drug-related AEs, AEs leading to trial drug discontinuation or serious AEs reported by patients was low and comparable between treatment groups and with the overall population.

Conclusion: Tiotropium Respimat® appears to be a generally safe add-on bronchodilator treatment option to ICS with or without other controllers in pediatric and adult black or African-American patients with asthma.

Clinical trial identifiers: NCT01634113, NCT01634139, NCT01634152, NCT01257230, NCT01277523, NCT01316380, NCT00350207, NCT01172808, NCT01172821, NCT01340209, NCT00772538, NCT00776984.

Among the estimated 300 million individuals affected by asthma worldwide [1], black patients have a higher disease burden and greater morbidity, with a higher rate of asthma-related emergency department visits, compared with other racial/ethnic groups [2]. Possible factors contributing to this include lower inhaled corticosteroid (ICS) use and limited access to preventive and specialist care [2]. To control symptoms and minimize future risk, the Global Initiative for Asthma recommends a stepwise approach for all patients [1]. As add-on therapy

* Corresponding author. Bridge Atlanta Medical Center, Norcross, Georgia, USA.
E-mail addresses: lmg254@gmail.com (L.M. Graham), h.a.m.kerstjens@umcg.nl (H.A.M. Kerstjens), christian.vogelberg@uniklinikum-dresden.de (C. Vogelberg), Eckard.Hamelmann@evkb.de (E. Hamelmann), Stanley.Szefler@childrenscolorado.org (S.J. Szefler), wendelgard.pisternick-ruf@boehringer-ingelheim.com (W. Pisternick-Ruf), michael.engel@boehringer-ingelheim.com (M. Engel), georges.el_azzi@boehringer-ingelheim.com (G. El Azzi), anna.unseld@boehringer-ingelheim.com (A. Unseld), immunotype@aol.com (M.B. Foggs).
[1] Dr El Azzi is currently employed by AstraZeneca LP.

https://doi.org/10.1016/j.rmed.2019.07.002
Received 31 January 2019; Received in revised form 10 May 2019; Accepted 1 July 2019
Available online 02 July 2019

Table 1
Exposure to trial medication and overview of adverse events in the black or African-American and overall populations with persistent asthma by treatment group for the two pools of placebo-controlled, parallel-group trials comparing 5 μg or 2.5 μg of tiotropium Respimat® with placebo Respimat® – all treated patients.

Pool of trials comparing tiotropium Respimat® 5 μg with placebo Respimat®				
	Overall population		Black or African-American population	
	Placebo Respimat®	Tiotropium Respimat® 5 μg	Placebo Respimat®	Tiotropium Respimat® 5 μg
Number of patients, N (%)	1889 (100.0)	1930 (100.0)	73 (100.0)	61 (100.0)
Exposure to trial medication, days				
Median (Q1, Q3)	170 (92, 337)	170 (93, 337)	170 (122, 336)	183 (166, 337)
Patients with any AEs[a], N (%)	1133 (60.0)	1116 (57.8)	54 (74.0)	38 (62.3)
Drug-related AEs[b]	66 (3.5)	89 (4.6)	3 (4.1)	2 (3.3)
AEs leading to discontinuation of trial drug	35 (1.9)	27 (1.4)	2 (2.7)	1 (1.6)
SAEs[c]	78 (4.1)	65 (3.4)	5 (6.8)	5 (8.2)
AEs reported in ≥10% of patients[d]				
Asthma[e]	549 (29.1)	469 (24.3)	27 (37.0)	22 (36.1)
Peak expiratory flow rate decreased	287 (15.2)	231 (12.0)	15 (20.5)	11 (18.0)
Upper respiratory tract infection	84 (4.4)	76 (3.9)	5 (6.8)	8 (13.1)
Nasopharyngitis	191 (10.1)	197 (10.2)	4 (5.5)	4 (6.6)
Pool of trials comparing tiotropium Respimat® 2.5 μg with placebo Respimat®				
	Overall population		**Black or African-American population**	
	Placebo Respimat®	Tiotropium Respimat® 2.5 μg	Placebo Respimat®	Tiotropium Respimat® 2.5 μg
Number of patients, N (%)	1307 (100.0)	1346 (100.0)	42 (100.0)	33 (100.0)
Exposure to trial medication, days				
Median (Q1, Q3)	168 (86, 183)	169 (86, 332)	170 (158, 173)	169 (161, 174)
Patients with any AEs[a], N (%)	715 (54.7)	735 (54.6)	27 (64.3)	18 (54.5)
Drug-related AEs[b]	41 (3.1)	45 (3.3)	1 (2.4)	0
AEs leading to discontinuation of trial drug	19 (1.5)	9 (0.7)	2 (4.8)	0
SAEs[c]	37 (2.8)	24 (1.8)	1 (2.4)	1 (3.0)
AEs reported in ≥10% of patients[d]				
Asthma[c]	300 (23.0)	255 (18.9)	8 (19.0)	7 (21.2)
Peak expiratory flow rate decreased	165 (12.6)	131 (9.7)	7 (16.7)	3 (9.1)
Nasopharyngitis	126 (9.6)	148 (11.0)	1 (2.4)	3 (9.1)

AE, adverse event; Q, quartile; SAE, serious adverse event.

[a] Any untoward medical occurrence (including an exacerbation of a pre-existing condition in a patient who received trial medication), which did not necessarily have to have a causal relationship with the trial medication.

[b] As assessed by the investigator considering all relevant factors, such as temporal relationship between administration of trial medication and onset of AE, dechallenge and rechallenge, as well as confounding factors, such as concomitant medication or concomitant diseases.

[c] Any AE that resulted in death, was immediately life-threatening, resulted in persistent or significant disability or incapacity, required or prolonged patient hospitalization, was a congenital anomaly or birth defect, or was to be deemed serious for any other reason.

[d] In either population in either treatment group.

[e] Represents asthma worsening or exacerbation.

to at least ICS, once-daily tiotropium Respimat®, a long-acting anticholinergic bronchodilator, has been shown to improve lung function and asthma control and to reduce asthma exacerbation risk in patients across different age ranges, with a safety profile comparable with placebo [3–6].

To assess the safety of tiotropium Respimat® compared with placebo Respimat® in black or African-American patients, we pooled data from 12 randomized, placebo-controlled, parallel-group, Phase II or III trials from the global Boehringer Ingelheim program with tiotropium Respimat® in asthma by two different doses of tiotropium: once-daily 5 μg (all 12 trials) or once-daily 2.5 μg (nine trials; Supplementary Table 1) [3–6]. In both pools, the safety results in black or African-American patients were compared with those in the overall population. The safety analysis considered treatment-emergent adverse events (AEs) with an onset after the first dose of trial medication until 30 days after the last dose. For each AE, the investigator was to provide the onset and end dates, the seriousness, the action taken with the trial medication, and an assessment of the relationship to the trial medication. Comparison of safety between the 5 μg and 2.5 μg doses of tiotropium was not an objective of this analysis.

Trial participants had symptomatic persistent asthma with a broad range of severities and were aged 1–75 years; trial duration was between 12 and 52 weeks. All trial medication was administered as add-on to ICS with or without other controller medications, such as long-acting β_2-agonists (LABAs) or leukotriene modifiers; therefore, placebo was equivalent to patients' background maintenance treatment (Supplementary Table 1).

Of the 5165 patients treated with either tiotropium or placebo across the 12 parallel-group trials in the global Boehringer Ingelheim program with tiotropium Respimat® in asthma, 167 (3.2%) were black or African American. In the 5 μg pool, 61 black or African-American patients were treated with 5 μg of tiotropium and 73 with placebo; in the 2.5 μg pool, 33 black or African-American patients were treated with 2.5 μg of tiotropium and 42 with placebo. Within both pools, baseline demographics and disease characteristics were generally balanced; numerical differences that were observed for some parameters between the treatment groups within a pool were not regarded as meaningful when considering the low number of black or African-American patients (Supplementary Table 2). Compared with the overall population, the black or African-American population in the 5 μg pool had a slightly lower lung function and asthma control (Supplementary Table 2). Median exposure to trial medication was generally comparable (Table 1).

In the black or African-American population, the proportion of patients reporting AEs was around 10% lower in the tiotropium groups than in the placebo groups in both pools (Table 1), and was generally comparable with the proportion of patients reporting AEs in the placebo and tiotropium groups in the overall population. The trend to a slightly

higher proportion of patients with AEs in the 5 μg tiotropium group in the black or African-American population compared with the overall population was likely due to slightly lower lung function and asthma control at baseline in the black or African-American population.

Within both pools, the number of black or African-American patients reported with investigator-assessed drug-related AEs, AEs leading to discontinuation of trial drug or serious AEs (SAEs) was low and comparable between treatment groups, and generally comparable with those in the overall population (Supplementary Table 3). None of the SAEs resulted in death. In the black or African-American population, no SAEs were reported in pediatric patients or adults with mild asthma; the few SAEs reported in adults with moderate or severe asthma in the tiotropium groups included 'asthma (worsening)' (five patients in the 5 μg group) and 'cervical radiculopathy' (one patient in the 2.5 μg group) (Supplementary Table 3). The proportion of patients with SAEs in the overall population was also low (Table 1).

Consistent with the overall safety profile of tiotropium Respimat® in pediatric and adult patients with asthma [7,8], the most frequently reported AEs in black or African-American patients in both pools were 'asthma', representing asthma worsening or exacerbation, and 'peak expiratory flow rate decreased', with generally comparable frequencies between both treatment groups. The observed higher frequency of these AEs compared with the overall population in the 5 μg pool was likely to be attributable to slightly lower lung function and asthma control at baseline in black or African-American patients compared with the overall population. 'Upper respiratory tract infection' was also reported in more than 10% of black or African-American patients in the 5 μg tiotropium group. Considering the relatively low number of black or African-American patients, a clinically relevant difference between the treatment groups was not observed for any reported AEs.

The safety of tiotropium from this analysis is consistent with the results from the BELT study ('Blacks and Exacerbations on LABA vs Tiotropium') [9], which showed a comparable safety and efficacy of tiotropium HandiHaler® and LABA when added to ICS in black adults with moderate-to-severe asthma. Whilst the limitation of our analysis is the restricted number of black or African-American patients included in the global trials, major strengths are that all trials were placebo-controlled, allowing the most valid comparison of treatment groups, and that the analysis included patients of all age ranges and asthma severities.

In conclusion, this pooled analysis supports tiotropium Respimat® as a generally safe add-on bronchodilator treatment option to ICS with or without other controllers in pediatric and adult black or African-American patients with asthma.

Acknowledgements

LeRoy Graham receives fees for serving as a speaker and member of a pediatric advisory board from Boehringer Ingelheim outside the submitted work. Huib Kerstjens reports an unrestricted research grant and fees for participation in advisory boards from Boehringer Ingelheim, paid to his institution; and advisory board participation fees from AstraZeneca, Chiesi, GlaxoSmithKline and Novartis, as well as an unrestricted research grant from Novartis and an unrestricted educational grant from GlaxoSmithKline outside the submitted work. Christian Vogelberg reports study-related payments to his institution from Boehringer Ingelheim during the conduct of the study; and personal fees for advisory boards and lectures from Boehringer Ingelheim and Novartis outside the submitted work. Eckard Hamelmann has nothing to disclose. Stanley Szefler reports fees from Boehringer Ingelheim, Genentech, GlaxoSmithKline, Aerocrine, Novartis, AstraZeneca, Daiichi Sankyo, Roche and Teva, and grants from GlaxoSmithKline outside the submitted work. Wendelgard Pisternick-Ruf, Michal Engel and Anna Unseld are employees of Boehringer Ingelheim. Georges El Azzi was an employee of Boehringer Ingelheim during the time of the study and manuscript development. He is currently an employee of AstraZeneca. Michael Foggs is a consultant for AstraZeneca, Boehringer Ingelheim and Genentech, and a speaker for AstraZeneca, Boehringer Ingelheim, Circassia, Genentech and Sanofi Aventis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2019.07.002.

Funding source

This work was supported by Boehringer Ingelheim.

References

[1] Global Initiative for Asthma, GINA Report: Global Strategy for Asthma Management and Prevention, (2018) http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/ , Accessed date: 22 October 2018.
[2] A.A. Ginde, J.A. Espinola, C.A. Camargo Jr., Improved overall trends but persistent racial disparities in emergency department visits for acute asthma, 1993-2005, J. Allergy Clin. Immunol. 122 (2008) 313–318.
[3] E. Hamelmann, S.J. Szefler, Efficacy and safety of tiotropium in children and adolescents, Drugs 78 (2018) 327–338.
[4] W.W. Busse, R. Dahl, C. Jenkins, et al., Long-acting muscarinic antagonists: a potential add-on therapy in the treatment of asthma? Eur. Respir. Rev. 25 (2016) 54–64.
[5] P. Paggiaro, D.M. Halpin, R. Buhl, et al., The effect of tiotropium in symptomatic asthma despite low- to medium-dose inhaled corticosteroids: a randomized controlled trial, J. Allergy Clin. Immunol. Pract. 4 (2016) 104–113 e2.
[6] K. Ohta, M. Ichinose, Y. Tohda, et al., Long-term once-daily tiotropium Respimat® is well tolerated and maintains efficacy over 52 weeks in patients with symptomatic asthma in Japan: a randomised, placebo-controlled study, PLoS One 10 (2015) e0124109.
[7] C. Vogelberg, E. Hamelmann, E. Vrijlandt, et al., Tiotropium add-on therapy has a safety profile comparable with that of placebo in children and adolescents with symptomatic asthma, Allergy 72 (2017) 414–415.
[8] R. Dahl, M. Engel, D. Dusser, et al., Safety and tolerability of once-daily tiotropium Respimat(®) as add-on to at least inhaled corticosteroids in adult patients with symptomatic asthma: a pooled safety analysis, Respir. Med. 118 (2016) 102–111.
[9] M.E. Wechsler, B.P. Yawn, A.L. Fuhlbrigge, et al., Anticholinergic vs long-acting beta-agonist in combination with inhaled corticosteroids in black adults with asthma: the BELT randomized clinical trial, J. Am. Med. Assoc. 314 (2015) 1720–1730.