

ORIGINAL ARTICLE

Combination budesonide/formoterol inhaler as maintenance and reliever therapy in Māori with asthma

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ABSTRACT

Background and objective: There are significant health disparities between Māori and non-Māori with asthma, a pattern seen between other ethnic populations. This study investigates outcomes for Māori in a randomized controlled trial (RCT) of combination budesonide/formoterol inhaler therapy in asthma.

Methods: This 24-week multicentre RCT recruited 303 adult asthma patients, 44 of whom were Māori. Participants were randomized to the single combination budesonide/formoterol inhaler as maintenance and reliever therapy ('SMART') regimen or 'standard' regimen (combination budesonide/formoterol inhaler for maintenance and salbutamol as reliever). Outcomes included patterns of beta-agonist inhaler use including 'high use' of reliever therapy (>8 actuations of budesonide/formoterol in excess of four maintenance doses per day for SMART and >16 actuations per day of salbutamol for standard). Differences in outcomes for Māori versus non-Māori were assessed using an interaction term between ethnicity and treatment.

Results: With adjustment for ethnicity, the SMART group had fewer days of high use (relative rate (RR) 0.57 (95% confidence interval (CI): 0.38–0.85)), days of high

SUMMARY AT A GLANCE

This 24-week randomized controlled trial demonstrates that the single combination budesonide/formoterol inhaler as maintenance and reliever therapy (SMART) regimen has a favourable risk/benefit profile in Māori, the indigenous people of New Zealand.

use without medical review within 48 h (RR 0.49 (95% CI: 0.32–0.75)) and severe exacerbations (RR 0.54 (95% CI: 0.36–0.81)) compared with standard. The magnitude of the benefit from the SMART regimen was similar in Māori and non-Māori. Regardless of treatment regimen, Māori demonstrated more days of high use, high use without medical review and underuse of maintenance therapy.

Conclusions: The SMART regimen has a favourable risk/benefit profile in Māori. Days of high use, days of high use without medical review and underuse of maintenance treatment were greater in Māori, regardless of treatment regimen.

Key words: asthma, health disparity, Māori, randomized controlled trial, single combination budesonide/formoterol inhaler as maintenance and reliever therapy.

Abbreviations: ACQ, Asthma Control Questionnaire; ED, emergency department; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long acting beta-agonist; Mcg, micrograms; RCT, randomized controlled trial; SMART, single combination budesonide/formoterol inhaler as maintenance and reliever therapy.

INTRODUCTION

Asthma is a leading cause of morbidity in New Zealand and contributes to a greater health burden among Māori (the indigenous people of New Zealand) compared with non-Māori New Zealanders.^{1,2} This

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includes increased prevalence,^{2,3} symptoms,^{3,4} asthma-related hospitalizations^{1,2,5–7} and deaths.^{1,5} The disproportionate impact of asthma related to ethnicity is not unique to New Zealand. Similar disparities have been reported in a number of at risk ethnic groups internationally, including in Australia,⁸ the United Kingdom,⁹ America¹⁰ and Canada.¹¹ There is evidence that barriers to health-care access^{7,12,13} and differing patterns in medication use^{1,7} contribute to these differences in asthma outcomes.

International studies suggest that treatment with the single combination budesonide/formoterol inhaler as maintenance and reliever therapy (SMART) regimen is associated with substantially fewer severe exacerbations in moderate-to-severe asthma than alternative regimens.^{14–16} The SMART regimen may therefore be of specific benefit to populations at increased risk of exacerbation, such as Māori. However, this regimen may potentially increase the risk of adverse effects due to exposure to high inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA) doses.

To investigate this, we recruited a substantive proportion of Māori in a randomized controlled trial (RCT) in which the SMART regimen was compared with a standard regimen (use of combination budesonide/formoterol inhaler for maintenance and salbutamol as a reliever) in patients at risk of severe exacerbations of asthma.¹⁷ In this manuscript, we report on the efficacy and safety of this regimen in Māori.

METHODS

RCT methods

The trial from which data for this analysis was collected was a 24-week open-label, prospective, multicentre RCT of SMART versus standard therapy in asthma patients aged 16–65 years (Australian and New Zealand Clinical Trials Registry number ACTRN12610000515099).¹⁷ Eligible participants had a current prescription for ICS and a physician's diagnosis of asthma with at least one asthma exacerbation in the preceding year. The main exclusion criteria were diagnosis of chronic obstructive pulmonary disease or respiratory symptoms that began after the age of 40 in participants with a ≥ 10 pack year smoking history. The study was undertaken at five centres in New Zealand (three general practice primary care centres, one Māori primary care clinic and one secondary care centre). The study protocol is available at http://www.mrinz.ac.nz/uploads/mrinz/SMART_Protocol.pdf.

All participants provided written informed consent and the study was approved by the New Zealand Multi-Region Ethics Committee (MEC/09/11/127). A computer-generated sequence randomized participants 1:1 to receive 200/6 micrograms (mcg) budesonide/formoterol via metered dose inhaler (Vannair, AstraZeneca Limited, Auckland, New Zealand; this is the metered dose inhaler formulation of the Symbicort dry powder inhaler (Turbuhaler)) with two actuations twice daily for maintenance and extra doses for relief of symptoms as per the SMART

regimen¹⁸ (SMART group) or 200/6 mcg budesonide/formoterol via metered dose inhaler two actuations twice daily for maintenance and salbutamol via metered dose inhaler (100 mcg per actuation – Ventolin, GlaxoSmithKline Limited, Auckland, New Zealand) for relief of symptoms (standard group). Written asthma self-management plans were provided and inhaler technique was checked at the first visit. Study visits took place at weeks 0 (randomization visit), 3, 10, 17 and 24.

All dispensed inhalers incorporated validated Smartinhaler Tracker (Nexus6 Limited, Auckland, New Zealand) electronic monitors, which recorded the date and time (to the nearest second) of each metered dose inhaler actuation.¹⁹ The monitors were used with a detailed trial quality control process.^{19,20} Participants were not aware of the monitors' capabilities in recording date and time. Detailed trial methodology has been reported elsewhere.^{17,20}

Māori recruitment

Māori health research consultation took place prior to study commencement (M.H.). Recruitment of Māori to the study was enhanced by involvement of a Māori primary care health clinic study site (Tu Kotahi Māori Asthma Trust). Māori researchers at the site (A.S. and C.D.) were involved in study design and created processes to aid Māori recruitment within the study protocol. Participants had the option to be seen in the Marae clinic (a clinic based at a traditional meeting house), at their workplace or in their home. Māori participants were assessed for eligibility and randomized to the study treatments on a subsequent day, by a Māori researcher (A.S.) and the clinical co-ordinating investigator for the study (M.P.).

Māori participants were also encouraged to participate at all other study sites.

Participants self-reported their ethnicity at the first study visit. New Zealand national guidelines were used to classify ethnicity for participants reporting more than one ethnicity by a standard system.²¹

Outcome measures

The primary outcome was the proportion of participants with at least one episode of high beta-agonist use ('high use'). This was defined as greater than eight actuations of budesonide/formoterol, additional to the four maintenance doses, per day (i.e. >12 actuations per day in total) in the SMART group and >16 actuations of salbutamol per day in the standard group. These definitions of high use were based on self-management plan values for beta-agonist use requiring medical review,^{18,22} and supported by the bronchodilator equivalence of 6 mcg formoterol to 200 mcg salbutamol with repeat dosing in acute asthma.^{23,24}

Other outcomes were: (i) number of days of high use; (ii) days of high use without medical review within 48 h; (iii) proportion of participants with 'marked overuse' (defined as >16 actuations per day of budesonide/formoterol in SMART or >24 actuations per day of salbutamol in standard) and number of

days of marked overuse; (iv) proportion of participants with 'extreme overuse' (defined as >20 actuations per day of budesonide/formoterol in SMART or >32 actuations per day of salbutamol in standard) and number of days of extreme overuse; (v) underuse of maintenance therapy ('underuse'): the proportion of participants with at least 1 day of ≤ 1 actuation of budesonide/formoterol and number of days of ≤ 1 actuations, and the proportion of participants with at least 1 day of 'non adherence' to maintenance therapy (defined as zero actuations of budesonide/formoterol in a day) and number of days of non adherence; (vi) severe asthma exacerbations:²⁵ the number of participants with at least one severe exacerbation (defined as the use of systemic corticosteroids for at least 3 days, or hospitalization or emergency department (ED) attendance due to asthma, requiring systemic corticosteroids), ED presentations for asthma and hospitalizations for asthma; (vii) corticosteroid exposure: the mean inhaled budesonide dose per day, total oral prednisone dose, number of courses of oral prednisone per year and composite systemic corticosteroid exposure per year; and (viii) other measures: forced expiratory volume in 1 s (FEV₁), percentage predicted FEV₁, and the Asthma Control Questionnaire (ACQ)-7 score.²⁶

Data analysis was by intention to treat. The general analysis strategy was to test an ethnicity-treatment interaction term for each outcome variable. If this was significant, $P < 0.05$, we planned to report the difference between SMART and standard for Māori and non-Māori separately. If the interaction term was not statistically significant, consistent with the relative effect of treatment being the same in Māori and non-Māori, we planned to report the difference in outcome for Māori versus non-Māori, adjusted for treatment, and the difference between treatments, adjusted for ethnicity. Only one outcome variable had a statistically significant interaction term and this is reported in the text of the results rather than in the tables. The specific analyses were calculation of odds ratios by logistic regression for dichotomous variables for at least 1 day of: overuse, marked overuse, extreme overuse, one or less budesonide/formoterol inhaler actuations per day and no budesonide/formoterol inhaler actuations per day; and at least one episode of: severe exacerbation, hospital or ED attendance requiring systemic corticosteroids, hospital attendance for asthma and ED attendance for asthma. Relative rates by Poisson regression with an offset for the observation time were used for the count variables including number of days of: high use, marked overuse, extreme overuse, one or less budesonide/formoterol inhaler actuations per day, no budesonide/formoterol inhaler actuations per day; and number of severe exacerbations and number of courses of oral corticosteroids. ANOVA was used for differences on the logarithm-transformed scale, where exponentiation is interpreted as mean ratios, for daily equivalent ICS use. Contingency table analysis was used for oral corticosteroid dose by creating three bands of use. For this outcome, the pre-specified plan had been to seek an appropriate transformation for the dose, such as the logarithm

transformation, or use a non-parametric method (the Mann-Whitney test), to compare the groups. After the data was collected, many participants had no oral prednisone use and both of these strategies were inappropriate. Continuous variables with appropriate data distributions were analysed by ANOVA: FEV₁, FEV₁ percentage predicted and ACQ-7. Spirometry was performed without instructions to participants to withhold their prescribed inhaled therapy.²⁵

The main trial aimed to recruit 300 participants and had 80% power, alpha 5%, to detect a relative risk of at least one episode of high use of 0.6 in relation to an anticipated rate of 36% in the standard arm. The subgroup analyses for Māori were pre-specified although we did not anticipate that we could recruit sufficient participants for the subgroup analysis to detect the nominated difference in the main outcome. This analysis is therefore exploratory. We have not adjusted for multiple statistical testing and present each analysis with 95% confidence intervals.

RESULTS

There were 303 participants who were enrolled between June 2010 and September 2011, of whom 44 were Māori (Fig. 1). Fifteen of the Māori participants were recruited at the Tu Kotahi Māori Asthma Trust site.

Twenty-five Māori were allocated to the SMART regimen and 19 to the standard regimen. At baseline, Māori participants had a greater number of previous hospital admissions, higher average ACQ-7 scores and smoking rates, and lower FEV₁ values (Table 1).

SMART versus Standard regimen, with adjustment for ethnicity

In keeping with results reported previously,¹⁷ with adjustment for ethnicity, the SMART regimen did not result in a significantly different proportion of participants with at least one episode of high, marked or extreme overuse when compared with the standard regimen (Table 2). However, the SMART group had a significant reduction in the number of days of high use, marked overuse, extreme overuse and the number of days of high use without medical review within 48 h (Table 2). The number of days of non-adherence to maintenance therapy was lower in the SMART group (Table 2).

With adjustment for ethnicity, there were fewer severe exacerbations in participants randomized to the SMART regimen (Table 3). Mean daily inhaled budesonide dose was higher in the SMART group, however oral prednisone dose was lower, resulting in no significant difference in the composite systemic corticosteroid exposure between the two regimens (Table 3).

Interaction with ethnicity

The only analyses with a statistically significant interaction term between treatment and ethnicity were ACQ-7 scores adjusted for baseline at visits 3 and 5 (both $P = 0.001$) (Table 3).

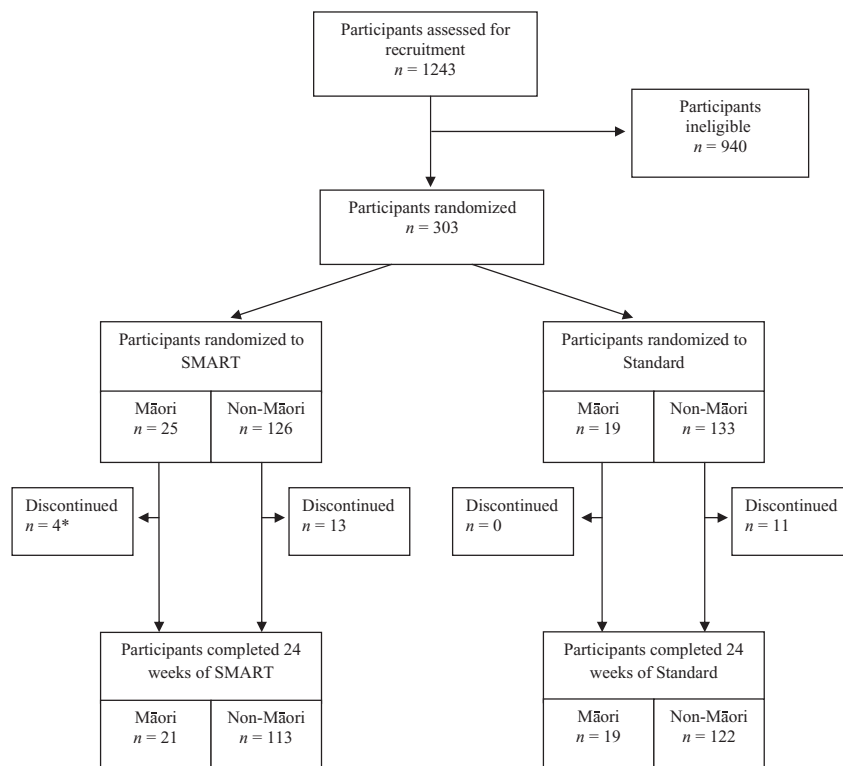


Figure 1 Flow of participants. *Four participants discontinued due to loss to follow up, worsening of asthma (participant decision), participant choice, worsening asthma (investigator decision).

Māori outcomes, adjusted for treatment

Independent of treatment allocation, Māori participants had worse outcomes as assessed by the proportion of participants with at least one episode of marked overuse and extreme overuse (Table 2). In addition, Māori demonstrated significantly more days of high, marked and extreme overuse (Table 2). In participants with at least one high use episode, the number of days of high use without medical review in the following 48 h was also significantly higher in Māori. Māori also had more days of ≤ 1 actuations and 0 actuations of maintenance therapy.

DISCUSSION

The SMART regimen was associated with a favourable risk/benefit profile compared with the standard regimen in Māori, with a similar efficacy to that in non-Māori. Regardless of regimen, Māori had a greater frequency of beta-agonist overuse, overuse without medical review and maintenance therapy underuse. We suggest that our findings are relevant to the clinical care of Māori and potentially other at risk populations.

The ACQ-7 score was the only outcome measure for which a significantly greater benefit was observed in Māori. At 24 weeks, the reduction (improvement) in ACQ-7 score with the SMART regimen in Māori and non-Māori were 1.01 and 0.10 respectively. This benefit is relevant as the minimal clinically important difference for ACQ-7 is 0.5²⁵ and symptom severity is greater in Māori than non-Māori,^{3,4} as reflected in the higher baseline ACQ-7 values in this study (Table 1).

Although analysis of whether the intervention had a different effect depending on Māori ethnicity was pre-specified, the trial was not primarily designed to detect differences between Māori and non-Māori. As is the case in subgroup analyses of controlled trials, this analysis may therefore lack statistical power to detect important differences by ethnicity. Another limitation is that this study examined a large number of outcome variables, which may inflate the type 1 error rate. The finding of a difference in ACQ-7 by Māori ethnicity should be interpreted cautiously because of this possibility.

The efficacy of the SMART regimen observed in Māori may apply to other at risk populations defined by ethnicity that have a disproportionate burden of disease.^{8–11} The efficacy of budesonide/formoterol in a fixed-dose regimen has been demonstrated in African American asthma patients,²⁸ and our study extends these findings to the use of budesonide/formoterol as maintenance and reliever therapy in another at risk ethnic group. Differences in response to LABA therapy by ethnicity have been suggested in African Americans²⁹ highlighting the importance of investigation into the impact of ethnicity on both individual and population-level outcomes in clinical trials.³⁰ Considered together with the Asian country subgroup analysis of the COSMOS study,³¹ our data show that the benefit of SMART in decreasing severe exacerbations may apply across a range of ethnic groups and health-care systems.

We observed that, independent of treatment regimen, Māori had increased rates of beta-agonist overuse and a significantly greater number of high use days without medical review. This has important

Table 1 Characteristics of trial participants

	Māori		Non-Māori	
	SMART <i>n</i> = 25	Standard <i>n</i> = 19	SMART <i>n</i> = 126	Standard <i>n</i> = 133
Age (years)	41.4 ± 13.1	39.4 ± 13.2	41.3 ± 13.9	43.1 ± 14.7
Male gender, <i>n</i> (%)	6 (24.0)	6 (31.6)	42 (33.3)	40 (30.1)
Duration of asthma (years)	30.2 ± 15.1	28.5 ± 12.5	26.0 ± 14.3	25.8 ± 14.9
ACQ-7 Score				
Mean	2.31 ± 0.96	2.17 ± 1.32	1.78 ± 0.94	1.86 ± 1.10
Band, <i>n</i> (%)				
≤0.75	0 (0.0)	2 (10.5)	20 (15.9)	22 (16.5)
0.75 to 1.5	5 (20.0)	4 (21.1)	29 (23.0)	35 (26.3)
≥1.5	20 (80.0)	13 (68.4)	77 (61.1)	76 (57.1)
Baseline FEV ₁ (L)	2.48 ± 1.17	2.38 ± 0.87	2.65 ± 0.85	2.52 ± 0.77
Baseline FEV ₁ % predicted	76.1 ± 19.8	75.0 ± 24.2	82.7 ± 18.6	81.2 ± 19.9
Severe exacerbation in the 12 months prior to recruitment, <i>n</i> (%)	23 (92.0)	18 (94.7)	114 (90.5)	123 (92.5)
Number of hospital admissions for asthma prior to recruitment, median (range)	2 (0 to 6)	2 (0 to 10)	1 (0 to 3)	1 (0 to 3)
ICS dose (mcg of budesonide or equivalent)	812.8 ± 395.1	1136.8 ± 405.8	802.9 ± 345.4	766.3 ± 342.3
LABA use, <i>n</i> (%)	15 (60.0)	15 (78.9)	77 (61.1)	88 (66.2)
Spacer use, <i>n</i> (%)	19 (76.0)	9 (47.4)	56 (44.4)	66 (49.6)
Pre-study use of a written asthma self-management plan, <i>n</i> (%)	4 (16.0)	5 (26.3)	11 (8.7)	15 (11.3)
Use of within-study symptoms-based plan	18 (72.0)	14 (73.7)	107 (84.9)	111 (83.5)
Use of within-study peak flow-based plan	7 (28.0)	5 (26.3)	19 (15.1)	22 (16.5)
Current smoker, <i>n</i> (%)	8 (32.0)	7 (36.8)	22 (17.5)	22 (16.5)
Pack year history, median (range)	10 (7.5 to 12)	8 (4 to 9)	5.5 (3 to 14.5)	10 (2 to 18)
	<i>n</i> = 8	<i>n</i> = 7	<i>n</i> = 22	<i>n</i> = 22
Ex-smoker, <i>n</i> (%)	11 (44.0)	7 (36.8)	38 (30.2)	41 (30.8)
Pack year history, median (range)	6.3 (1 to 15)	10 (4 to 20)	5 (1.8 to 9.0)	3 (2 to 9)
	<i>n</i> = 11	<i>n</i> = 7	<i>n</i> = 38	<i>n</i> = 41
Non-smoker, <i>n</i> (%)	6 (24.0)	5 (26.3)	66 (52.4)	70 (52.6)

n values as per column heading unless otherwise stated. Plus-minus values are means ± SD. ICS dose conversion: 500 mcg fluticasone = 800 mcg budesonide, 1000 mcg beclomethasone = 800 mcg budesonide.

ACQ, Asthma Control Questionnaire; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long acting beta-agonist; mcg, micrograms; *n*, number.

health implications as overuse of beta-agonist therapy during a severe exacerbation with associated delay in receiving medical care is recognized as a factor that contributes to risk of asthma death.^{32,33} Māori also had increased rates of underuse of maintenance medication. Health literacy skills are poorer in Māori than non-Māori;³⁴ and non-adherence to asthma treatment recommendations is ever more attributed to reduced, or inadequate, health literacy, which prevents a person from accessing, understanding, evaluating and communicating asthma-related information.³⁵ This and the implications of socioeconomic status on outcome were not able to be addressed by this study.

Previous interventional studies in Māori with asthma have shown the implementation of asthma self-management plans based on regular ICS use improve health outcomes.^{36–39} This study extends these findings by demonstrating that combination ICS/LABA inhaler therapy also improves outcomes, and that the benefit is greater when implemented in the SMART rather than the standard regimen.

A strength of this study is our consultation with Māori researchers during its design and the ongoing commitment to recruiting patients through a Māori health provider. This resulted in 15% of the study's participants identified as Māori, similar to the proportion of Māori in the general New Zealand population.⁴⁰

In conclusion, this study has shown that the SMART regimen has a favourable risk/benefit profile in Māori with asthma. Overall, the SMART regimen had similar efficacy in Māori and non-Māori, although a greater improvement in asthma control with the SMART regimen was observed in Māori. We suggest that these findings may be generalizable to other at risk populations defined by ethnicity which have a similar disproportionate burden of disease.

Acknowledgements

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Table 2 Results for medication use outcomes

Outcome	Māori		Non-Māori		Māori versus non-Māori	SMART versus Standard
	SMART (n = 25)	Standard (n = 19)	SMART (n = 126)	Standard (n = 133)		
High use						
At least one episode of high use, n (%)	16 (64.0)	12 (63.2)	68 (54.0)	56 (42.1)	Odds ratio 1.9 (0.95 to 3.6) <i>P</i> = 0.07	1.5 (0.96 to 2.4) <i>P</i> = 0.07
Number of days of high use	8.0 ± 14.4	19.4 ± 38.3	4.5 ± 14.2	7.4 ± 16.8	Relative rate 0.57 (0.38 to 0.85) <i>P</i> = 0.006	—
Number of days of high use in participants with at least one high use episode	12.5 ± 16.4 <i>n</i> = 16	30.8 ± 44.9 <i>n</i> = 12	8.3 ± 18.6 <i>n</i> = 68	17.6 ± 22.3 <i>n</i> = 56		
Number of days of high use without medical review in participants with at least one high use episode	12.4 ± 16.2 <i>n</i> = 16	27.4 ± 38.5 <i>n</i> = 12	7.6 ± 18.1 <i>n</i> = 68	16.3 ± 20.7 <i>n</i> = 56	Odds ratio 1.71 (1.06 to 2.73) <i>P</i> = 0.03	0.49 (0.32 to 0.75) <i>P</i> = 0.001
Marked overuse						
At least one episode of marked overuse, n (%)	13 (52.0)	11 (57.9)	41 (32.5)	45 (33.8)	Odds ratio 2.4 (1.3 to 4.7) <i>P</i> = 0.007	0.92 (0.57 to 1.48) <i>P</i> = 0.72
Number of days of marked overuse	4.0 ± 7.6	13.4 ± 33.6	2.4 ± 10.6	3.6 ± 9.4	Relative rate 0.54 (0.35 to 0.85) <i>P</i> = 0.007	—
Number of days of marked overuse in participants with at least one marked overuse episode	7.7 ± 9.4 <i>n</i> = 13	23.1 ± 42.3 <i>n</i> = 11	7.3 ± 17.7 <i>n</i> = 41	10.7 ± 13.6 <i>n</i> = 45		
Extreme overuse						
At least one episode of extreme overuse, n (%)	10 (40.0)	9 (47.4)	31 (24.6)	31 (23.3)	Odds ratio 2.4 (1.2 to 4.7) <i>P</i> = 0.009	1.0 (0.60 to 1.68) <i>P</i> = 0.99
Number of days of extreme overuse	2.4 ± 4.3	10.0 ± 31.1	1.4 ± 7.0	1.9 ± 5.5	Relative Rate 0.53 (0.33 to 0.86) <i>P</i> = 0.01	—
Number of days of extreme overuse in participants with at least one extreme overuse episode	6.0 ± 5.0 <i>n</i> = 10	21.1 ± 43.7 <i>n</i> = 9	5.7 ± 13.4 <i>n</i> = 31	8.0 ± 9.2 <i>n</i> = 31		
Underuse of maintenance budesonide/formoterol treatment						
At least one day of zero actuations, n (%)	20 (80.0)	17 (89.5)	100 (79.4)	109 (82.0)	Odds ratio 1.14 (0.74 to 1.75) <i>P</i> = 0.57	0.79 (0.44 to 1.41) <i>P</i> = 0.43
Number of days of no actuations	42.7 ± 47.4	49.6 ± 50.0	20.2 ± 27.5	31.3 ± 41.3	Relative rate 1.79 (1.31 to 2.45) <i>P</i> < 0.001	0.72 (0.55 to 0.94) <i>P</i> = 0.01
At least one day of one or less actuation, n (%)	21 (84.0)	18 (94.7)	108 (85.7)	114 (85.7)	Odds ratio 1.14 (0.70 to 3.89) <i>P</i> = 0.59	0.88 (0.46 to 1.69) <i>P</i> = 0.70
Number of days with one or less actuations	44.2 ± 48.2	51.3 ± 51.3	25.7 ± 31.6	34.8 ± 43.4	Relative rate 1.57 (1.15 to 2.14) <i>P</i> = 0.005	0.79 (0.61 to 1.02) <i>P</i> = 0.07

n values as per column heading unless otherwise stated. Plus-minus values are means ± SD. Odds ratios and relative rates are reported with 95% confidence intervals. Estimates are weighted as part of the analysis and may be numerically different to the values calculated from the tabulated mean values. The relative rates of days of overuse and underuse, by treatment group and Māori ethnicity, were estimated by Poisson regression with an offset for the length of treatment exposure. The analysis suggested overdispersion and a dispersion term was used to adjust for this.

n, number.

Table 3 Severe asthma exacerbations, corticosteroid exposure and efficacy outcomes

Outcome	Māori		Non-Māori		Māori versus non-Māori	SMART versus Standard
	SMART (n = 25)	Standard (n = 19)	SMART (n = 126)	Standard (n = 133)		
Severe asthma exacerbations						
Participants with at least one severe exacerbation, n (%)	4 (16.0)	7 (36.8)	24 (19.0)	43 (32.3)	1.02 (0.48 to 2.15) P = 0.97	Odds ratio 0.46 (0.27 to 0.79) P = 0.005
Number of severe exacerbations, (weighted mean rate per year)	0.39 ± 0.93	1.20 ± 1.87	0.62 ± 1.72	0.92 ± 1.49	1.06 (0.62 to 1.81) P = 0.83	Relative Rate 0.54 (0.36 to 0.81) P = 0.003
Hospital and ED attendances for asthma						
Participants with at least one hospital admission or ED attendance, n (%)	0 (0.0)	2 (10.5)	7 (5.6)	7 (5.3)	0.85 (0.19 to 3.89) P = 0.83	Odds Ratio 0.78 (0.28 to 2.15) P = 0.63
Participants with at least one hospital admission, n (%)	0 (0.0)	0 (0.0)	2 (1.6)	2 (1.5)	—	1.01 (0.14 to 7.24) P = 0.99
Daily ICS dose†						
Daily budesonide dose, mcg	1514 ± 3501	725.3 ± 391.7	829.5 ± 512.1 n = 125	678.4 ± 391.5 n = 132	0.97 (0.84 to 1.26)§ P = 0.77	Ratio of Means 1.22 (1.06 to 1.41) P = 0.006
Oral corticosteroid dose††						
Oral corticosteroid dose, mg	48.8 ± 136.9	136.3 ± 236.8	83.3 ± 256.0	125.2 ± 399.2	See text for description of analysis*	
Number of courses of oral corticosteroids per year of follow-up	0.60 ± 1.56	1.42 ± 2.42	0.84 ± 2.68	1.10 ± 1.83 n = 132	1.10 (0.67 to 1.79) P = 0.71	Relative Rate 0.58 (0.40 to 0.84) P = 0.004
Composite systemic corticosteroid exposure (ICS plus oral)††						
Composite systemic corticosteroid exposure, mg prednisone equivalent per year	773.3 (643.4)	800.1 (517.5)	797.8 (937.1) n = 125	768.1 (1120.8) n = 132	1.02 (0.79 to 1.31) P = 0.88	Ratio of Means 1.03 (0.86 to 1.22) P = 0.77

Table 3 Continued

Asthma control and lung function			
Māori		Non-Māori	
SMART minus Standard adjusted for baseline: Mean difference (95% confidence interval)		SMART minus Standard adjusted for baseline: Mean difference (95% confidence interval)	
SMART	Standard	SMART	Standard
ACQ-7§§			
Visit 1	2.31 ± 0.96	1.78 ± 0.94	1.86 ± 1.10
Visit 2	1.11 ± 0.74 n = 25	1.23 ± 0.80 n = 125	1.38 ± 1.02 n = 131
Visit 3	0.99 ± 0.65 n = 23	1.14 ± 0.75 n = 120	1.25 ± 0.90 n = 128
Visit 4	1.12 ± 0.80 n = 21	1.01 ± 0.75 n = 118	1.36 ± 1.04 n = 122
Visit 5	0.94 ± 0.62 n = 20	1.05 ± 0.79 n = 115	1.21 ± 0.96 n = 123
FEV ₁ (L)†††			
Visit 1	2.48 ± 1.17	2.65 ± 0.85	2.52 ± 0.77
Visit 5	2.68 ± 1.2 n = 19	2.82 ± 0.86 n = 114	2.66 ± 0.95 n = 122
FEV1 % predicted†††			
Visit 1	76.1 ± 19.8	82.7 ± 18.6	81.2 ± 19.9
Visit 5	82.0 ± 21.0 n = 19	87.9 ± 16.2 n = 114	84.8 ± 22.3 n = 122
		2.2 (−0.7 to 5.0) P = 0.14	
		—	
		0.04 (−0.06 to 0.15) P = 0.40	
		—	
		−0.17 (−0.30 to 0.068) P = 0.21	
		−0.07 (−0.26 to 0.11) P = 0.44	
		−0.31 (−0.52 to −0.11) P = 0.003	
		−0.10 (−0.31 to 0.11) P = 0.36	

Data summaries are mean ± standard deviation. Odds ratios and relative rates are reported with 95% confidence intervals. The weighted mean rate per year is the total number of events in the study group/total person follow-up time in years for the study group. Relative rates were calculated by Poisson regression with an offset of the logarithm of the period of observation (for the analyses of severe exacerbation, hospital admission, ED attendance and number of courses of systemic corticosteroid), unless otherwise stated. *n* values are as per the column heading unless otherwise stated.

† The logarithm of the annualized ICS use was the response variable in a weighted normal linear model, with the randomized treatment as a predictor and the treatment exposure time as a weight (individuals with longer periods of treatment exposure were given more weight and those with shorter periods of treatment exposure less weight in the analysis).

‡ Ratio of mean values of annualized corticosteroid use (exponent of the difference in logarithms of SMART minus standard).

§ Corticosteroid conversion: 100 mg intravenous hydrocortisone = 25 mg oral prednisone.

* Parametric and non-parametric analyses were not valid because of a large number of zero values.

† Budesonide dose was converted to prednisone equivalent dose, based on a bioequivalence conversion calculated in a prior study (5000 mcg budesonide = 10 mg prednisone).^{17,27} The sum of the prednisone equivalent dose and systemic corticosteroid dose was annualized. The logarithm of the annualized steroid use was the response variable in a weighted normal linear model, with the randomized treatment as a predictor and the treatment exposure time as a weight (individuals with longer periods of treatment exposure were given more weight and those with shorter periods of treatment exposure less weight in the analysis).

§§ ACQ-7 was analysed by a mixed linear model examining response profiles at each time point using random effects for individual subjects and an unstructured covariance pattern to account for correlation between measurements on the same subjects which forces a common intercept and adjusts for baseline values. The P-value for the interaction term between ethnicity and outcome by treatment was statistically significant, *P* = 0.001, consistent with the difference in the response of Māori and non-Māori to the SMART and Standard regimens.

††† FEV₁ and FEV₁ % predicted were analysed by a mixed linear model examining response profiles at each time point using random effects for individual subjects and an unstructured covariance pattern to account for correlation between measurements on the same subjects which forces a common intercept and adjusts for baseline values.

ACQ, Asthma Control Questionnaire; ED, emergency department; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; mcg, micrograms; *n*, number.

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