

Patch testing of budesonide in Italy: the SIDAPA baseline series experience, 2018-2019

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Budesonide, corticosteroids, patch test, skin tests, SIDAPA baseline series

Abstract

Background: Budesonide was included in the European Baseline Series in 2000 as the most suitable marker for CS hypersensitivity. In the last 2 decades a decreasing trend of budesonide allergy was observed.

Objectives: To estimate the prevalence of positive patch test reactions to budesonide in an Italian large patch test population characterizing patients according to MOAHLFA index and evaluating the benefit with extended readings of budesonide patch test.

Methods/Patients: Retrospective analysis of patient demographics and patch test results over a 2-year period (2018-2019) was performed at 14 patch test Clinics in Italy.

Results: Ninety patients among 14544 (0.6%) reacted to budesonide 0.01%. Positive reactions were mild in 54.4% and late readings at D7 showed new positive reactions in 37.8% of patients. MOAHLFA index showed a significant positive association with male gender, atopic dermatitis, and age > 40 years and a significant negative association with hand and face dermatitis.

Conclusions: We documented a low prevalence of budesonide allergy in Italy, confirming its decreasing trend recently reported in literature. Nevertheless, budesonide needs to be maintained in the baseline series for its good ability to detect CS sensitization.

1 | INTRODUCTION

Despite budesonide was firstly described as contact sensitizer in a patient affected by psoriasis already in 1980¹, corticosteroid (CS)-induced allergic contact dermatitis (ACD) was considered rare before the 90s. Successively, this molecule has been one of the CSs most widely implicated in ACD, occasionally for its use in aerosol form.² Starting from the 90s, several studies demonstrated that CS-induced ACD is much more common than originally thought,^{3,4} and budesonide was identified as the most suitable marker for CS hypersensitivity.⁵ In 2000 an EECDRG multicenter study on 2599 consecutive dermatitis patients patch tested with budesonide at different concentrations demonstrated that 1.0% of patients reacted to at least one concentration and 76.9% of them reacted to budesonide 0.01%. Therefore, this concentration was indicated as optimal, also to minimize the risk of patch-test sensitization,⁶ and budesonide 0.01% was recommended to be included in the European Baseline Series.⁷

In the last 20 years, some studies focused on the prevalence of positive patch test reactions to budesonide 0.01% in consecutive patients,⁸⁻¹² ranging from 1.8% in a North American study⁸ conducted in 2003-2004 in 5141 patients to 0.6% in a Spanish study conducted in 2015-2016 in 3699 patients.¹²

Herein, we conducted a multicenter retrospective study on budesonide 0.01% patch testing with the aims to (i) estimate a two-year period prevalence of positive patch test reactions in an Italian large study group, (ii) characterize positive patch test patients according to MOAHLFA, the acronym for male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg dermatitis, facial dermatitis, and age >40 years, and (iii) evaluate the benefit with extended readings of budesonide patch test.

2 | METHODS

Data from 14 Italian Dermatology clinics homogenously distributed in Italy were collected during a 2-year period between January 2018 and December 2019. Patients (n= 14554, 5204 males; mean age 48.0 years) consecutively patch tested with the SIDAPA (Società Italiana Dermatologia Allergologica Professionale Ambientale) baseline series containing budesonide 0.01% pet were enrolled. Patch testing (40 mg/cm² pet.) was performed with the Haye's Test Chambers® (Haye's Service B.V., Alphen aan den Rijn, The Netherlands) on Soffix® tape (Artsana, Grandate, Italy), and allergens from FIRMADiagent® (Florence, Italy). Readings were performed on day (D)2, D4, and D7;¹³ patients were asked to return if there were new late reactions beyond D7.¹⁴

The clinical relevance of positive budesonide patch test was determined based on fulfilling the following criteria: patient's history of possible exposure to budesonide or other corticosteroids, clinical skin examination, and remission of dermatitis after the patient stopped using corticosteroids. Among budesonide-positive patients, those who had never been exposed to budesonide were carefully questioned in order to precise if other CS molecules could be responsible for contact dermatitis. Patients who reported contact dermatitis to other CS molecules were patch tested with the suspected molecules and those with positive patch test reactions¹⁵ were classified as cross-reacting patients.

Prevalence of budesonide allergy was stratified according to age groups, gender, scoring of positive reactions, also focusing on new positive D7 patch test reactions. Demographics and clinical characteristics defined by the MOAHLFA index were analysed, as well as the presence of concomitant steroid sensible diseases, the route of sensitization, and the clinical morphology of contact allergy to budesonide or cross-reacting corticosteroids.

The X² test with Yates' continuity correction and Fisher's exact test were used to analyse categorical variables. Statistical analysis was performed using IBM-SPSS® version 25.0 (IBM Corp., Armonk, NY, USA, 2017). In all analyses, a two-sided *P* value ≤ .05 with Bonferroni correction was considered significant.

3 | RESULTS

Among 14544 patch tested patients, 90 (0.6%) reacted to budesonide 0.01%. This prevalence was higher in males than in females (0.8% vs 0.5%, respectively; $P = .0517$). Clinical relevance was documented in 70 subjects (77.8%), more frequent in males (80.5%) than in females (75.5%) ($P = .5$) (Table 1). Among the 70 patients with relevant positive patch test reactions, 55 (78.6%) presented contact dermatitis to budesonide, while 15 (21.4%) had never been exposed to budesonide and reported contact dermatitis to other CS molecules. Further patch testing with these latter suspected molecules documented positive reactions to topical (hydrocortisone 17-butyrate 8, clobetasol propionate 3, halcinonide 1) and systemic (methylprednisolone 1, triamcinolone acetonide 1, dexamethasone 1) CSs. These patients were classified as cross-reacting patients. Occupational exposure was documented in 1 patient (F, 39), a nurse presenting acute hand dermatitis after contact with methylprednisolone infusion.

Prevalence of budesonide allergy stratified according to age groups was higher for subjects older than 50 years (55/5829, 0.9%) than in those younger (35/8725, 0.4%) ($P = .00004$). In particular, the highest prevalence was documented in the age groups 51-60 (26/2446, 1.1%) and >70 (15/1425, 1.1%), while in the age group 61-70, prevalence was 0.7% (14/1958). Among young patients, the lowest prevalence was observed in the age group 31-40 (9/2938, 0.3%), followed by <31 (10/2805, 0.4%) and 41-50 (16/2982, 0.5%) (Figure 1). Males older than 50 years showed higher prevalence (27/2137, 1.3%) than females over 50 (28/3692, 0.8%) ($P = .05$), especially in the age group 51-60 (males: 14/879, 1.6%; females 12/1567, 0.8%; $P = .06$). According to age groups and gender, relevant positive reactions were observed more frequently in males aged 51-60 (13/14, 92.9%) and less frequently in males aged 31-40 (1/3, 33.3%) (Figure 1).

Cross-reactions to budesonide were observed more frequently in over 70 (6/11, 54.5%), followed by 31-40 (2/5, 40.0%) and 41-50 (4/11, 36.4%), while they were absent in the youngest age group (Figure 2).

Considering the reading time, all positive reactions were collected within D7 and no further positive reactions were collected beyond D7. A total of 34/90 (37.8%) positive patch tests were observed only in D7; this percentage was higher in positive patch tests with clinical relevance (32/70, 45.7%) than in those without clinical relevance (2/20, 10.0%) ($P = .003669$) (Table 2). Strong (++) and extreme (+++) positive reactions were observed in 41/90 (45.6%) patients, higher in non-relevant (11/20, 55.0%) than in relevant positive reactions (30/70, 42.9%) ($P = .3362$).

Twenty-two patients (24.4%) were mono-sensitized to budesonide, while 68/90 (75.6%) showed

at least one concomitant positive patch test reaction, mostly to nickel sulphate (19/90, 21.1%), fragrance mix I (13/90, 14.4%), *Myroxylon Pereirae* (7/90, 7.8%), potassium dichromate (6/90, 6.7%), and methylisothiazolinone (5/90, 5.6%).

According to the MOAHLFA index, crude analysis showed in patients with budesonide allergy a significant association with atopic dermatitis and age > 40 years (positively) and occupational, hand, and face dermatitis (negatively). However, in an adjusted regression model, male gender was positively associated to budesonide allergy while occupational dermatitis lost significant association (Table 3).

Concomitant steroid sensible diseases in subjects with relevant positive reactions to budesonide were atopy (45/70, 64.3%), particularly atopic dermatitis (40/70, 57.1%) and rhino-conjunctivitis and/or asthma (32/70, 45.7%), followed by chronic eczema (13/70, 18.6%) and psoriasis (6/70, 8.8%) (Table 4). Route of sensitization was mostly cutaneous (49/70, 70.0%), followed by inhalator (18/70, 25.7%).

4 | DISCUSSION

The first case of ACD due to budesonide¹ was reported only 1 year after its marketing as topical and systemic anti-inflammatory drug.¹⁶ In the following 10 years, few other single cases were reported,^{2,17-19} and the first study on routinely budesonide patch tested patients was performed by Goossens et al in 1991.⁴ In this study, among 710 consecutive patients tested with budesonide 1% ethanol, a prevalence of 3.0% of positive reactions was reported and budesonide was defined not only as marker of CS allergy but also as a sensitizer itself.⁴ In 2000 budesonide 0.01% in pet. was included in the European Baseline Series⁷ and several multicenter studies demonstrated a decreasing trend in the following 15 years in Europe (Baeck et al,⁹ 1.6%; Reduta et al,²⁰ 1.4%; Madsen et al,²¹ 1.2%; Vind-Kezunovic et al,²² 1.0%) and North America (Warshaw et al,⁸ 1.8%; Warshaw et al,²³ 0.8%). In the last 5 years, 2 multicenter studies performed by GEIDAC (2015-16)¹² and ESSCA (2015-18)²⁴ showed a further decreasing trend of this prevalence (0.62% and 0.67%, respectively).

Our study conducted on 14554 consecutive patch tested patients in a two-year period (2018-19) provides a large data set on budesonide allergy. The prevalence of 0.6% documented in this study confirms the gradual and continuous reduction of budesonide allergy observed in the last 2 decades.^{8,9,12,20-24} This decreasing trend could be due to a decreased prescription of budesonide for cutaneous use²⁵ but also probably of other cross-reacting CSs such as hydrocortisone-17-butyrate (S isomer of budesonide), the Dermatologists' knowledge of budesonide contact allergy,²⁶ the availability of new topical CS molecules with better pharmacokinetic profile,^{27,28} and the marketing of topical non-steroidal immunomodulators (pimecrolimus, tacrolimus).²⁹ In view of this, older patients have been more exposed to budesonide during their lifetime than the younger ones, and this could explain the significant higher prevalence of budesonide allergy among subjects older than 50 years (0.9%), observed also in Danish²² and Spanish¹² populations. Moreover, among all patch tested subjects we observed a higher prevalence in males (0.8%) than in females (0.5%), confirming the recent ESSCA data (0.84% and 0.6%, respectively),²⁴ particularly in males aged between 51-60 years (1.6%).

Among the 90 positive patch test reactions to budesonide, 77.8% were judged clinically relevant. This data was lower than that reported by NACDRG in patch tested patients in 2007-2008 (88.9%)¹¹ and 2009-2010 (91.3%)²³ and recently in New Zealand (100%).³⁰ This discrepancy could depend on the fact that the NACDRG studies took into account not only definite and probable relevance but

also possible relevance. Regarding the New Zealand study, the number of positive budesonide reactions among patch tested patients was very low (6/319).³⁰

The results of our study confirm that cross-reactions between budesonide and other CSs are an issue.^{9,12,31-35} In fact, 16.7% of positive patch test reactions to budesonide were considered cross-reactions, with the highest prevalence in >70 age group. These patients never used this CS and patch test resulted positive with clinical relevance to topical and systemic CSs belonging to Baeck³³ group 1 in 60.0% (hydrocortisone 17-butyrate 8, methylprednisolone 1), group 2 in 13.3% (halcinonide 1, triamcinolone acetonide 1), and group 3 in 26.7% (clobetasol propionate 3, dexamethasone 1). Despite these data seem to confirm budesonide as a good marker to detect the majority of patients sensitized to topical and systemic CSs,^{7,9} we can not draw a definite conclusion as the study design did not include an additional CS series in the whole study group.

The intrinsic anti-inflammatory properties of budesonide may influence the patch test results in terms of scoring and late reactions. Regarding to scoring, we observed extremely strong reactions only in 10.0% of positive patch test reactions, while in 54.4% of cases, reactions were mild, confirming ESSCA study data on budesonide (55.1%).²⁴ We can not explain why strong positive reactions were observed more frequently among non-relevant than relevant positive reactions. Moreover, contact allergy to budesonide would have been missed in 37.8% of our patients without the D7 reading, confirming that late reading is mandatory in CS patch testing.⁴ Surprisingly, we observed a higher percentage of new positive reactions on D7 for reactions with clinical relevance.

Among factors influencing sensitization to budesonide, in addition to the already mentioned male gender, we found relevant positive association with atopic dermatitis and age > 40 years. This could be explained by a long-standing use of CSs in adults affected by concomitant steroid sensitive diseases such as atopy, chronic eczema, and psoriasis.⁹ On the other hand, we found relevant negative association with face dermatitis, probably due to physicians' and patients' awareness of the potential non-immunologic side effects such as steroid induced rosacea and perioral dermatitis.³⁶ Surprisingly, we also found relevant negative association with hand dermatitis in budesonide positive patients, in contrast to what reported in Danish²² and New Zealand³⁰ populations. The negative association with hand dermatitis observed by us is likely influenced by our low prevalence of occupational dermatitis, which is often associated with ACD of the hands.³⁷ In fact, in our entire study population of 14554 patients we observed a prevalence of occupational dermatitis of only 7.8%, in contrast to what reported by European²⁴ and North American^{8,11} studies. We did not observe any relationship to leg dermatitis, a frequently reported predisposing

factor,^{9,22,30} probably due to prescription habits among Italian Dermatologists for leg ulcers and stasis dermatitis.

Regarding sensitization routes, the majority of our patients was sensitized by cutaneous exposure (70.0%), confirming literature data,⁹ even if the inhalator route was more frequent (25.7%) than previously reported^{9,38} due to the increasing use of budesonide-containing products for nasal and oral inhalation in Italy.³⁹

In conclusion, our multicenter study documented in Italy a low prevalence of budesonide allergy, confirming its decreasing trend reported in literature in the last 2 decades. Despite this, we emphasize the need of maintaining budesonide 0.01% in the baseline series for its good ability to detect CS sensitization, also being a good marker to identify cross-reactions with systemic CSs, preferentially belonging to Group 1 and 2, including several systemic CSs available on the market. However, budesonide rarely detects sensitization to group 3 molecules. Moreover, budesonide is still largely used as nasal spray or inhalation for allergic rhinitis, asthma, and chronic obstructive lung diseases as it ensures a good symptom control as maintenance therapy reducing exacerbations.⁴⁰ Recently, budesonide stepped into the spotlight for the management of persistent hyposmia in COVID-19 patients⁴¹ and for its efficacy when early administrated by inhalation to reduce the likelihood of needing urgent medical care and the time to recovery following early SARS-CoV-2 infection.⁴²

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- Accepted Article
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TABLE 1 Positive patch test reactions to budesonide 0.01% in 14554 consecutive patch tested patients (5204 men, 9350 women)

	Total			Male			Female		
	N.	%	Mean age (ys)	N.	%	Mean age (ys)	N.	%	Mean age (ys)
Total positive reactions	90	0.6	53.7	41	0.8	54.2	49	0.5	53.3
Relevant reactions	70	77.8	54.4	33	80.5	54.0	37	75.5	54.6
Cross reactions	15	21.4	59.3	6	18.2	66.5	9	24.3	54.9
Non-relevant reactions	20	22.2	51.3	8	19.5	53.6	12	24.5	49.5

TABLE 2 Scoring of positive patch test reactions to budesonide 0.01% in 90 patients

Scores	Positive reactions (%)				Relevant positive reactions (%)				Non-relevant positive reactions (%)			
	+	++	+++	Tot	+	++	+++	Tot	+	++	+++	Tot
D4 pos	25 (27.8)	25 (27.8)	6 (6.6)	56 (62.2)	17 (24.3)	17 (24.3)	4 (5.7)	38 (54.3)	8 (40.0)	8 (40.0)	2 (10.0)	18 (90.0)
D4 neg/D7pos	24 (26.7)	7 (7.8)	3 (3.3)	34 (37.8)	23 (32.8)	6 (8.6)	3 (4.3)	32 (45.7)	1 (5.0)	1 (5.0)	0	2 (10.0)
Total	49 (54.4)	32 (35.6)	9 (10.0)	90 (100)	40 (57.1)	23 (32.9)	7 (10.0)	70 (100)	9 (45.0)	9 (45.0)	2 (10.0)	20 (100)

TABLE 3 The MOAHLFA index for patients with patch test positivity to budesonide

	Budesonide patch test				Chi square test (crude) <i>P</i> -value	Logistic regression [OR (95% CI)]
	Positive		Negative			
	N = 90	%	N = 14464	%		
M	41	45.6	4715	32.6	.009	1.64 (1.07-2.50)
O	1	1.1	1126	7.8	.007	0.17 (0.02-1.24)
A	50	55.6	5202	36.0	.0001	3.08 (2.01-4.71)
H	9	10.0	4432	30.6	.00002	0.22 (0.11-0.44)
L	8	8.9	1376	9.5	.841	0.61 (0.29-1.27)
F	8	8.9	3653	25.3	.004	0.21 (0.10-0.44)
A	71	78.9	9002	62.2	.001	2.52 (1.50-4.23)

Significant associations are reported in bold.

M, male; O, occupational dermatitis; A, atopic dermatitis; H, hand dermatitis; L, leg dermatitis; F, face dermatitis; A, age > 40 years; CI, confidence interval; OR, odds ratio.

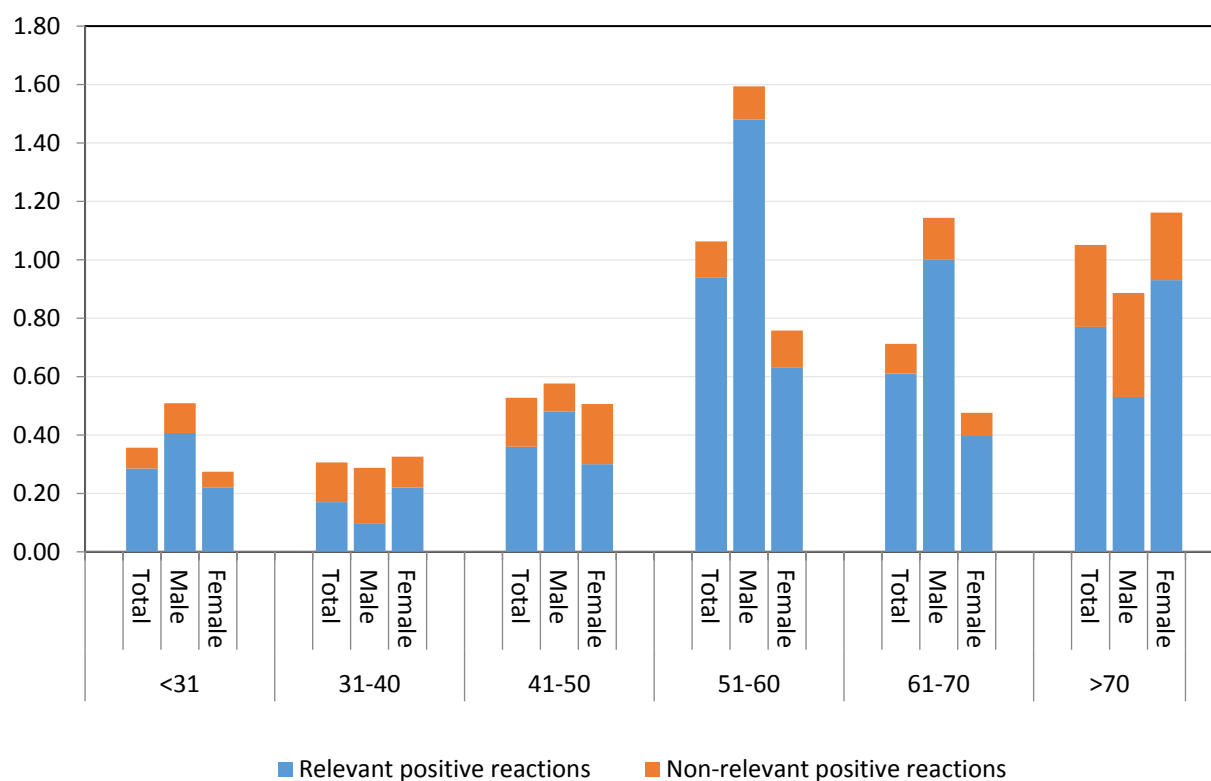
TABLE 4 Subjects with relevant positive reactions to budesonide (70): concomitant steroid sensible diseases and route of sensitization

	Total (70)		M (33)		F (37)	
	N.	%	N.	%	N.	%
Concomitant steroid sensible diseases						
Atopy	45	64.3	18	54.5	27	73.0
Atopic dermatitis	40	57.1	15	45.5	25	67.6
Rhino-conjunctivitis, asthma	32	45.7	13	39.4	19	51.4
Chronic eczema*	13	18.6	4	12.1	9	24.3
Psoriasis	6	8.8	4	12.1	2	5.4
Hemorrhoids/rhagades	4	5.7	3	9.1	1	2.7
Others**	7	10.0	3	9.1	4	10.8
Route of sensitization						
Cutaneous	49	70.0	21	63.6	28	75.7
Inhalator	18	25.7	10	30.3	8	21.6
Muco-cutaneous (anal/perianal)	3	4.3	2	6.1	1	2.7

* Allergic contact dermatitis (7), irritant contact dermatitis (4), stasis dermatitis (2).

** Chronic urticaria (3), chronic obstructive pulmonary disease (2), lichen planus (1), parapsoriasis (1).

FIGURE 1 Prevalence of contact sensitivity to budesonide 0.01% in 90 subjects according to age and gender: relevant and non-relevant positive reactions



Total patients patch tested: <31 ys: 2805; 31-40 ys: 2938; 41-50 ys: 2982; 51-60 ys: 2446; 61-70 ys: 1958; >70 ys: 1425

FIGURE 2 Prevalence of relevant positive patch test reactions to budesonide 0.01% in 70 subjects according to age: sensitivity induced by budesonide and cross reactions to budesonide

