Pharmacy Benefits Management Strategic Healthcare Group

Medical Advisory Panel

Drug Class Review: Orally Inhaled Steroids

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The standard screening test for determining relative anti-inflammatory potencies for inhaled corticosteroids has been the topical vasoconstriction (McKenzie skin blanching) test. The existing comparative clinical trials of asthma efficacy and systemic activity generally reflect the standard in vitro measures of potency. Existing data confirm only a potency difference, not an efficacy difference between inhaled steroids. The relative anti-inflammatory potency of the inhaled corticosteroids is in the following rank order: [1-4]

flunisolide = triamcinolone < beclomethasone = budesonide < fluticasone

Inhaled steroid	Dosage forms	Puffs/ canister	Low dose mcg/day	Medium dose mcg/day	High dose mcg/day	# /month medium dose	Cost/ Inhaler ($)	$/month medium dose
Flunisolide 250mcg	MDI	100	500-1000	1000-2000	>2000	1-2	2.88	2.88-5.78
Triamcinolone 100mcg	MDI with built-in spacer	240	400-1000	1000-2000	>2000	1-2	18.09	18.09-36.18
Beclomethasone 42mcg	MDI	200	168-504	504-840	>840	2-3	3.62	6.98-10.48
Budesonide 200mcg	DPI	200	200-600	600-1000	>1000	0.5-1	69.08	34.54-69.08
Fluticasone	MDI, DPI	120	88-264	264-660	>660			
(MDI)	(blister packs)							
44mcg						2-4	19.88	39.76-79.52
110mcg						1-2	29.03	29.02-58.06
220mcg						0.5-1	50.65	25.32-50.65
(DPI)								
50mcg		60 doses					21.32	for low-dose use
100mcg							27.95	
250mcg						0.5-1.5	35.98	18-53.97

Flunisolide, budesonide, and fluticasone are administered twice daily; beclomethasone and triamcinolone may be administered twice daily or 3-4 times daily Dose per National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 2:Guidelines for the Diagnosis and Management of Asthma

Studies

The table below summarizes comparative trials between agents. Small studies, pediatric studies, abstracts, and studies using dosage forms not available in the U.S. have been excluded. These studies demonstrate that when equal potency dosing is used, efficacy is similar.

Study	Study patients	Dose	Results	Comments
Fabbri 1993[5] R, DB, MC, Pr N=274 1 year	Moderate-severe asthma Receiving 1000-2000mcg/day of inhaled BDP or BUD	BDP MDI 750mcg bid vs. FP MDI 750mcg bid ± spacers could ↑ to 1000mcg bid if needed	FEV1: FP>BDP a.m. PEF: FP>BDP p.m. PEF: FP>BDP beta-agonist: FP>BDP SS: FP=BDP, fewer asthma exacerbations with FP	Used FP at twice the potency of BDP
Lundback 1993[6] R, DB, DD, MC, Pr N=585 6 weeks with 46-wk open label follow up	Moderate asthma Receiving 400-1000mcg of inhaled steroid (type not specified)	BDP MDI 500mcg bid vs. FP MDI 250mcg bid vs. FP DPI 250mcg bid	FEV1: FP=BDP a.m. PEF: FP=BDP p.m. PEF: FP=BDP beta-agonist: FP=BDP SS: FP>BDP nighttime FP<BDP daytime	Used equipotent doses of BDP and FP
Barnes 1993[7] R, DB, SD, MC, Pr N=154 6 weeks	Severe asthma receiving 1500-2000mcg/day of an inhaled steroid	BDP MDI 1000mcg bid vs. FP MDI 500mcg bid	FEV1: FP=BDP a.m. PEF: FP=BDP p.m. PEF: FP=BDP beta-agonist: FP=BDP SS: FP=BDP % pred PEF: FP>BDP	Used equipotent doses of BDP and FP

BDP=beclomethasone diproprionate; BUD=budesonide; CO=crossover; DB=double-blind; DD=double dummy; DPI=dry powder Inhaler; FLU=flunisolide; FP=fluticasone proprionate; MC=multicenter; MDI=metered-dose inhaler; O=open; PC=placebo controlled; Pr=parallel; R=randomized; SD=single dummy; SS=subjective symptoms; TAA=triamcinolone acetonide, TD= triple dummy

Dahl 1993[8] R, DB, MC, Pr N=672 4 weeks	Moderate asthma requiring BDP or BUD ≤ 1000mcg/day	BDP MDI 200mcg bid vs. FP MDI 50mcg vs. 100mcg vs. 200mcg vs. 400mcg bid No spacers used	PEF: ↑ linearly with FP; FP 200= BDP 400 Beta agonist: BDP=FP all doses Sympt-free days: FP400 similar to BDP400 Asthma exacerbations: BDP 400=FP 100 and 200 BDP>FP 400; BDP> FP 800	Efficacy was similar when equipotent doses of BDP and FP were compared.
Leblanc 1994[9] R, DB, MC, Pr N=261 4 weeks	Mild-moderate asthma	BDP MDI 200mcg bid vs. FP MDI 100mcg bid ± spacers	FEV1: FP=BCP a.m. PEF: FP=BCP p.m. PEF: FP=BCP beta-agonist: FP=BCP SS: FP=BCP	Used equipotent doses of BDP and FP
Langdon 1994[10] R, O, MC, Pr N=275 8 weeks		BUD DPI 400 mcg bid vs. FP DPI 200 mcg bid	a.m. PEF: FP>BUD beta-agonist: FP=BUD SS: FP=BUD	Used medium dose for both agents
Lorentzen 1996[11] R N=213 12 months	Severe chronic asthma currently receiving inhaled steroids 1000-2000mcg/day	FP MDI 1000mcg/day vs. BDP MDI 2000mcg/day	FEV1: FP=BDP PEF: FP=BDP	Used equipotent doses of BDP and FP
Anderson R, DB, DD, PC, MC, Pr N=321 8 weeks		TAA MDI 400mcg bid vs. BDP 200mcg bid	FEV1: BDP=TAA>Pl a.m. PEF: BDP=TAA>Pl beta-agonist: BDP=TAA>Pl SS: BDP=TAA>Pl	Used equipotent doses of BDP and TAA **Data on file. Schering/Key Pharmaceuticals, Inc. and FDA**
Aaronson R, DB, DD, PC, MC, Pr N=313 8 weeks		TAA MDI 400mcg bid vs. BDP 200mcg bid	FEV1: BDP>TAA>Pl a.m. PEF: BDP=TAA>Pl beta-agonist: BDP=TAA>Pl SS: BDP=TAA>Pl	Used equipotent doses of BDP and TAA **Data on file. Schering/Key Pharmaceuticals, Inc. and FDA**
Condemi 1997[12] R, DB, DD, PC, MC, Pr N=291 24 weeks	FEV1 50-80% predicted Maintained on BDP or TAA	TAA MDI 200mcg qid vs. FP DPI 250mcg bid	FEV1: FP>TAA>Pl a.m. PEF: FP>TAA>Pl beta-agonist: FP>TAA>Pl withdrew from lack of efficacy: Pl>TAA>FP	Low dose TAA being compared to medium dose FP
Bergmann 1997[13] R, MC, Pr N=169 6 weeks	Mild-moderate asthma FEV1/FVC ≥ 60% predicted	FLU MDI 500mcg bid vs. FP DPI 250mcg bid	FEV1: FP>FLU a.m. PEF: FP>FLU p.m. PEF: FP>FLU SS: FP>FLU	Low dose FLU being compared to medium dose FP
Pauwels 1998[14] R, DB, MC, CO N=306 12 months	Moderate-severe asthma, FEV1 ≥ 40% predicted Receiving BDP or BUD 800-2000mcg/day	BDP MDI 1000mcg/ FP MDI 500mcg daily vs. BDP MDI 1500mcg/FP MDI 750mcg daily vs BDP MDI 2000mcg/FP MDI 1000mcg daily ± large volume spacer	FEV1:FP=BDP a.m. PEF: FP > BDP p.m. PEF: FP=BDP beta-agonist: FP=BDP SS: FP=BDP	Used equipotent doses of BDP and FP No wash-out period between the crossover pts. randomized into 1 of 3 arms based on prior steroid dose
Bronsky 1998[15] R,DB,DD,PC,MC, Pr N=328 56-day	Mild-moderate persistent asthma FEV1 50-90% predicted while on inhaled steroid	BDP MDI 168mcg bid vs. TAA MDI 400mcg bid No spacer used in BDP group	FEV1:BDP=TAA>Pl a.m. PEF: BDP=TAA>Pl p.m. PEF: BDP=TAA>Pl beta-agonist: BDP=TAA>Pl SS:BDP>TAA>Pl	Used equipotent doses of BDP and TAA
Berkowitz 1998[16] R,DB,DD,PC,MC, Pr N=339 56-day	Mild-moderate persistent asthma FEV1 50-90% predicted while on inhaled steroid	BDP MDI 168mcg bid vs. TAA MDI 400mcg bid No spacer used in BDP group	FEV1:both active groups > Pl a.m. PEF: both active groups > Pl p.m. PEF: both active groups > Pl beta-agonist: both active groups > Pl SS: both active groups > Pl	Used equipotent doses of BDP and TAA

Gross 1998[17] R, DB, DD, PC, MC, Pr N=304 24 week	FEV1 50-80% predicted Receiving BDP or TAA 8-12 puffs daily ≥ 4 weeks	TAA MDI 200 mcg qid vs. FP DPI 250mcg bid	FEV1: FP> TAA>Pl a.m. PEF: FP> TAA>Pl beta-agonist: FP> TAA>Pl withdrew from lack of efficacy: Pl>TAA>FP	Low dose TAA being compared to medium dose FP
Heinig 1999[18] DB,DD, Pr N=395 24 weeks	Severe asthma requiring inhaled steroids	BUD DPI 2000mcg/day vs. FP DPI 2000mcg/day	FEV1: FP > BUD SS: FP> BUD Asthma exacerbations: FP=BUD	
Baraniuk 1999[19] R, DB, TD, MC, Pr N=680 12 week	FEV1 40-85% predicted Receiving BDP 252-672 mcg/day, TAA 600-1000mcg/day, or FLU 1000mcg/day for ≥ 3 months	FP MDI 220 mcg bid vs. FP MDI 88mcg bid + salmeterol 42 mcg bid vs. TAA MDI 600mcg bid	FEV1=FP + salmet > FP > TAA a.m. PEF= FP+salmet = FP>TAA p.m. PEF= FP+salmet = FP>TAA beta-agonist= FP+salmet = FP>TAA SS= FP+salmet = FP>TAA	Medium doses of TAA and FP compared to low dose FP + salmeterol
Newhouse 2000[20] R, MC N=176 6 week	Moderate asthma FEV140-85% predicted Receiving BDP, FP, or BUD 800-2000mcg/day	FLU via AeroChamber 750mcg bid vs. BUD DPI 600mcg bid	FEV1: FLU=BUD a.m. PEF: FLU=BUD p.m. PEF: FLU=BUD beta-agonist: FLU=BUD SS: FLU=BUD	Medium dose FLU compared to high dose BUD

Adrenal suppression[21-27]

The best tests for evaluating basal adrenocorticol activity are the 24-hour integrated measurement of plasma cortisol level or the 24-hour urinary free cortisol excretion (24hr/UFC). These tests are impractical for routine monitoring and are therefore, typically used in a controlled laboratory research environment. The overnight or early morning urinary cortisol-creatinine ratio (UCC) has been shown to be as sensitive as the integrated 24-hour urinary free cortisol. The AM plasma cortisol level is the least sensitive test. To evaluate adrenal cortical reserve in response to stress, the ACTH or Cosyntropin stimulation test is used. The 1mcg ACTH test is more sensitive than the standard 250mcg short test because physiologic rather than pharmacological doses are used. Studies that use test subjects with asthma/COPD rather than normal volunteers and chronic dosing rather than single dose is preferred.

Studies using the 24hr/UFC, UCC or ACTH stimulation test have been reviewed. Many of the subjects with asthma had been on inhaled steroids prior to the study. In general, inhaled steroids used at low-moderate doses for less than 1 year do not seem to cause HPA-suppression. Short-term use (4-8 weeks) of high doses may result in abnormal ACTH stimulation values in some patients. There is little information on long-term, low-dose inhaled steroids, but one study suggests that the short ACTH stimulation test remains normal.

Effects on bone [22,28-29]

Qualitative CT or dual energy x-ray absorptiometry (DXA) scan at the hip and spine are reliable measures of bone mineral density (BMD). Of the two techniques, DXA is preferred. When evaluating studies, one also needs to take into account the age of the patient (eg. post-menopausal females) and previous oral steroid use.

Results from studies that evaluated low-moderate doses over 1-2 years, ranged from no change to 1.1% spine and 1.7% hip decreases in BMD. Results of low-moderate doses for ≥3 years ranged from no changes to decreased lumbar BMD in one study and 2% ↓ femoral neck in another study.

Results from studies that evaluated high doses over 1-2 years, ranged from no change to decreased BMD at the femoral neck. Results of high doses for >3 years resulted in decreased hip and lumbar BMD.

CFC-free inhalers

Through the Clean Air Act and the Montreal Protocol, the United States Government has committed to eliminate the use of CFC containing metered dose inhalers. Currently, MDIs fall under the essential-use designation. This means a CFC containing product cannot be removed unless the following criteria are met:

- at least 2 different CFS-free products available for an active moiety if an active moiety is marketed under multiple NDA's or exists in multiple strengths (at least one CFC-free product for drugs under a single NDA or available in one strength)
- same route of administration
- same indication(s)
- approximately the same level of convenience of use compared to the product(s) containing CFCs
- adequate supplies and production capacity
- at least 1 year of post marketing data for each product
- persuasive evidence showing patient acceptance of the alternative product

The FDA believes it is premature to set a specific time frame for the elimination of CFC containing products because, many variables exist as to when new products will be submitted to the agency for review, when they gain approval, and when the products might be considered clinically acceptable.

Currently, there are only two CFC-free products (excluding dry powder inhalers) on the market. Qvar® (beclomethasone HFA) and Proventil HFA® (albuterol HFA). Qvar, which will be handled by MacNeil Pharmaceuticals, is available in the 40 and 80mcg strengths (100 puffs/canister) and priced at $19.34 and $26.62 respectively. Because of the smaller particle size, more drug is delivered to the lungs, therefore Qvar is dosed at half the beclomethasone CFC dose. Proventil HFA is manufactured by Schering and is available in the 90mcg strength (200 puffs/canister) and priced at $13.76.

It may be another 3-5 years before we begin seeing a phase-out of some CFC inhalers. Nevertheless, it may be prudent to begin anticipating the added cost to the VA for CFC-free products. As an example, in FY2000, 2,981,490 albuterol and 589,958 beclomethasone inhalers were dispensed at total cost of $4.9 and $2.1 million dollars respectively. If the HFA products are dispensed at the prices previously mentioned, the cost per year will rise to $41 million for albuterol and $11.5 million for beclomethasone. Although the prices for the other products are not known at this time, we can be fairly certain that they will be higher than those paid by VA for currently marketed products. The table below reviews the currently marketed products and the status for a CFC-free product.

Current MDIs on the market

DRUG	TRADE NAME	STRENGTHS/ $ PER INHALER	COMMENTS
Corticosteroids			
Beclomethasone	Vanceril (Schering) Beclovent (Glaxo)	42, 82 mcg $3.62/27.73	Beclomethasone HFA (Qvar) available in 40 and 80 mcgs
Flunisolide	Aerobid	250 mcg $2.88	Flunisolide HFA submitted to FDA
Triamcinolone	Azmacort	100 mcg $18.09	Triamcinolone HFA submitted to FDA
Fluticasone	Flovent	44, 110, 220 mcg $19.88/29.03/50.65	Dry powder diskus inhaler available; CFC-free MDI in Phase III trials with NDA expected to be filed in 2002.
Bronchodilators			
Albuterol	Proventil (Schering) Ventolin (Glaxo) Several generics	90 mcg $1.65	Proventil HFA available in 90 mcg; capsules for inhalation by Rotahaler available; HFA MDI in Phase III trials (Glaxo) with NDA expected to be filed in 2002.
Salmeterol	Serevent	25 mcg $35.28	Dry powder diskus inhaler available; CFC-free MDI in Phase III trials with NDA expected to be filed in 2002.
Metaproterenol	Alupent	0.65mg $13.37	Studies in CFC-free vehicles in progress, MFR uncertain when NDA will be filed
Pirbuterol	Maxair	0.2 mg $17.13	Plans to go forward with the HFA technology, but has no plans as to when NDA will be filed
Terbutaline	Brethaire, Bricanyl	0.2 mg	Discontinued
Bitolterol	Tornalate	0.37 mg	Discontinued
Ipratropium	Atrovent	18mcg $18.45	Studies in CFC-free vehicles in progress, MFR uncertain when NDA will be filed
Ipratropium/ albuterol	Combivent	18/90 mcg $21.16	Studies in CFC-free vehicles in progress, MFR uncertain when NDA will be filed

Mast cell stabilizers			
Cromolyn	Intal	800 mcg $26.70	Per Aventis, there are no plans at this time to go forward with a CFC-free product
Nedocromil	Tilade	1.75 mg $16.64	Per Aventis, there are no plans at this time to go forward with a CFC-free product

HFA-hydrofluoroalkane

Discussion/recommendations

There is little difference in efficacy and toxicity when equipotent doses of inhaled steroids are administered. To achieve equipotent doses between lower potency and higher potency agents require that a greater number of inhalations be administered thus, possibly influencing patient compliance.

1. Flunisolide should be considered as the first-line choice for patients requiring a lower potency agent for the following reasons:
    - Clinically similar to beclomethasone and triamcinolone
    - Considerably less costly than triamcinolone ($2.88 versus $18.09)
    - Availability of beclomethasone is not guaranteed

2. Flunisolide is presently the only orally inhaled product on National Formulary; addition of second agent will be considered at a later date.

3. Fluticasone should be reserved for patients whose symptoms are not adequately controlled with maximum dosing with lower potency agents or patients who have difficulty complying with a lower potency agent that requires a large number of inhalations.

4. Review the CFC-free products separately as more products become available.

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