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Opinion

Viscous Fluticasone in Eosinophilic Esophagitis: a Suitable Step Forward

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Abstract

Eosinophilic esophagitis (EoE) is a chronic immune mediated disease of the esophagus whose incidence has risen rapidly and is now the first cause of dysphagia in the adult population. Symptoms significantly impact on quality of life and the chronic inflammation, if left untreated, can lead to fibrosis and strictures. Fluticasone propionate (FP) and budesonide (BUD), currently represent one of the first-line therapy for EoE and their efficacy has been demonstrated in multiple studies. However, no current FDA-approved medications exist in the United States, while an orodispersible budesonide tablet was officially approved in Europe but is still unavailable in many Countries. This has led to the routine "off label" use of swallowed metered-dose inhaler with suboptimal delivery. Oral viscous budesonide (OVB) has proved superior to swallowed nebulizer formulation because of a longer drug mucosal contact time. The use of BUD in the form of OVB has gradually surpassed the use of FP. Data on inhaled glucocorticoids, however, have shown that FP has better pharmacological characteristics than BUD resulting in a higher therapeutic index. Comparison between FP and BUD has been established solely using FP nebulizer vs OVB. In clinical trials, FP has been tested only in the form of swallowed spray and oro-dispersible tablets. Only two studies have published data on powder based FP viscous preparations, but liquid-based viscous FP solutions might have a higher potential and clinical data are absent from literature. Viscous suspensions proved to be non-inferior to esophagus-specific targeted budesonide formulations. Until more standardized esophagus-targeted formulations become easily available, there is a need to ameliorate topical steroids formulations with wide availability. Fluticasone viscous solutions have the potential of meeting these needs and would deserve more clinical evidences to support its clinical use. Moreover, possible alternative viscous mediums to sucralose, such as honey or xanthan gum should be considered.

Keywords: Eosinophilic Esophagitis; Fluticasone; Budesonide; Oral Viscous Budesonide; Swallowed topical steroids

Abbreviations: EoE: Eosinophilic Esophagitis; STC: Swallowed Topical Corticosteroids; PPI: Proton Pump Inhibitor, FED: Food-Elimination-Diets, FP: Fluticasone Propionate; BUD: Budesonide; MDI: Metered-Dose Inhaler; OVB: Oral Viscous Budesonide

Introduction

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disease of the esophagus characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation [1,2]. EoE can affect all age groups, with an incidence peak between the third and the fifth decade of life. Since its first recognition in the '70s, EoE incidence has risen rapidly over the last 15 years both in the US [3] and in Europe [4,5] and is now recognized as the first cause of dysphagia in the adult population [6].

The main clinical manifestation of EoE in adults is dysphagia and food impaction after ingestion of solid foods. In children and infants EoE symptoms might be subtler with failure to thrive, vomiting, nausea, regurgitation, abdominal pain, food aversion and feeding problems [7,8]. Natural history studies revealed that EoE is a chronic disease that significantly impacts on quality of life, including vitality and general health scores [9] and, if left untreated, results in continued inflammation [10] and consequent complications such as fibrosis and strictures [11].

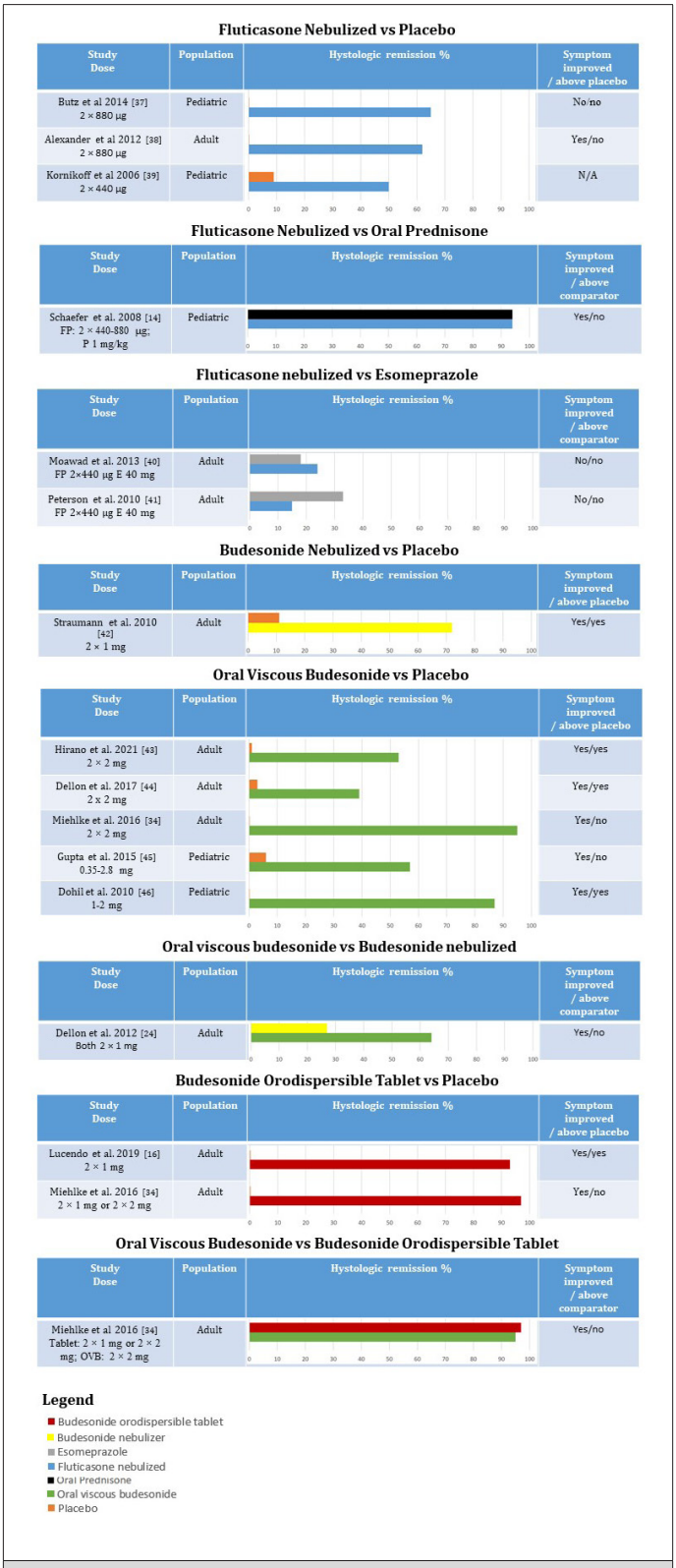

Figure 1: summarizes results from randomized clinical trials assessing efficacy of topical steroids in EoE.

Figure1 Abbreviations: OVB: Oral Viscous Budesonide; FP: Fluticasone propionate; E: esomeprazole; P: Prednisone.

Corticosteroids have been the first treatment for EoE since its recognition as a distinct disease [12]. At first, systemic steroids were employed but subsequent studies demonstrated that topical steroids were able to achieve comparable results, carrying a lower risk of systemic adverse effects [13,14]. Swallowed topical corticosteroids (STC) currently represent one of the first-line therapy for EoE, together with proton pump inhibitor (PPI) and food-elimination-diets (FED) [2] and remain today one of the most efficacious therapeutic approach in both children and adults [15]. Multiple studies have demonstrated that STC are able to decrease clinical symptoms, improve histological features of the disease inducing histologic remission in 39%-100% of patients [10,16-18], to reverse EoE transcriptome [19] and even decrease fibrosis [20]. Reported adverse effects were mucosal esophageal candidiasis (described in up to 10% of patients) and rarely adrenal axis suppression, bone demineralization, and diminished growth [21,22].

Fluticasone propionate (FP) and budesonide (BUD) are the most studied and used molecules for EoE treatment in literature (Figure 1). However, no current FDA-approved medications exist for the treatment of EoE in the United States [16,23], while an orodispersible budesonide tablet (Jorveza®) was officially approved in June 2018 in Europe for EoE induction therapy but is still unavailable in many Countries, such as Italy. This has led to the routine "off label" administration of preparations for bronchial or intranasal delivery, mainly in the form of asthma metered-dose inhaler (MDI) administered to the esophagus by swallowing. The swallowed use of an aerosolized compound can be challenging and can lead to a variable amount of the active drug being deposited into the upper and lower airways and in the ambient air with suboptimal delivery and less than ideal targeting of esophageal mucosa [24]. Moreover, given the high prevalence of concomitant asthma with EoE, patients may habitually continue to inhale the MDI or might follow standard instructions on inhalation techniques provided with the drug.

Thus, a particular budesonide-based preparation, named oral viscous budesonide (OVB), created by mixing liquid budesonide intended for nebulized administration with sucralose or other viscous agents to create a slurry consistency, was developed and has proved superior to the same amount of drug delivered by swallowing a nebulized mist [24] with a longer drug mucosal contact time confirmed scintigraphically. The use of BUD in the form of OVB has, since then, risen and gradually surpassed the use of FP, also for the publication of retrospective and prospective data assessing its superiority in terms of histological and clinical response [25, 26].

However, data on inhaled glucocorticoids used in asthma have shown that FP has a higher potency than BUD, with a higher receptor affinity [27,28]. Moreover, FP has demonstrated a lower bioavailability than BUD, longer lung retention times and a higher dose to which a 20% systemic cortisol suppression have been shown, thus resulting in a higher therapeutic index [29]. These properties have not yet been demonstrated in the esophagus, but it feels rational to postulate that FP may behave similarly in EoE therapy, making it the most effective and safe molecule of the pair. Direct comparison between FP and BUD has been established solely using fluticasone nebulizer vs OVB [25,26], and the superiority of OVB on FP could be explained not by its intrinsic anti-inflammatory properties but by the more prolonged contact between the mucosa and the medication due to the sucralose utilized in OVB, just as demonstrated by the previous study comparing BUD suspension and spray formulation [30]. In clinical trials, FP has been tested only in the form of swallowed spray and lately oro-dispersible tablets [31]. Up to date, only two studies, both retrospective, have published data on fluticasone preparations, both powder based, aimed to increase esophageal delivery. Kia et al. [32] proposed an orally administered powder formulation of fluticasone and described a decrease of eosinophilic peak densities to < 15 eos/hpf in 75% of patients, together with improvement in dysphagia symptoms and endoscopic findings of furrows and exudates [32]. Ketchem et al. [33] formulated a viscous suspension by mixing powdered fluticasone with a Methocel gel reporting significant improvement in EoE clinical and endoscopic findings, with trend towards improvement in eosinophil counts. This is notable because the cohort was composed by three-quarters of patients previously non responders to STC (mostly budesonide or fluticasone spray) and/or FED. In particular, 35% of these patients achieved histological remission (<15 eos/hpf) with compounded fluticasone treatment.

These data are surely of great interest with promising results and in addition the ease of stock and transportation of a powder formula is surely alluring. However, liquid-based viscous FP might have a higher potential for drug delivery even if clinical data are still absent from literature. Viscous suspensions proved to be non-inferior to esophagus-specific targeted budesonide formulations (effervescent tablet for orodispersible use) in a European phase-II-multicenter trial with a randomized, double blind, double-dummy, placebo-controlled design, although the effervescent formulation was preferred by patients due to ease of use [34].

Until more standardized esophagus-targeted formulations of topical steroids become commercially available, there is a need to develop and ameliorate the esophageal delivery of topical steroids formulations that could be maximally effective and safe. Moreover, possible alternative viscous medium to sucralose, a non-absorbable sugar with potential of gastrointestinal symptoms at high doses, should be considered. For example, some reports exist on the efficacy of honey- and xanthan gum-based solutions. In particular, these articles reported comparable mucosal contact time and higher palatability of honey based solutions [35,36] and a higher mucosal contact time with comparable palatability of xanthan gum-based formula [36] compared to sucralose-based formula. Based on the clinical and pharmacological evidence reported above, we believe that fluticasone viscous solutions have the potential of meeting the mentioned needs and would deserve more clinical evidences to support and finalize its clinical use [37-46].

Conflict of Interest

The Authors do not declare any conflict of interest

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