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(RESEARCH ARTICLE)

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Meta-analysis of the role of steroids in Eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis (EoE) is a chronic, immune-mediated inflammatory disease of the esophagus that manifests as eosinophil-predominant infiltration. Swallowed topical steroids have been the preferred medications for EoE as they relieve symptoms and restore the pathology. This meta-analysis comprehensively examined whether steroid application is the best therapy for histologic, cell morphologic, and endoscopic findings compared to placebo in eosinophilic esophagitis.

A literature search was conducted on various medical databases to identify relevant randomized controlled trials (RCTs) that compared topical steroid therapy with placebo to treat EoE. The principal endpoints of the study were histological response, clinical response rate, and endoscopic response rates.

Meta-analysis was carried out with the help of the RevMan software, which utilized odds ratios with 95% confidence intervals for dichotomous diseases.

In the meta-analysis, nine trials with 193 participants combined were considered. Topical corticosteroids were significantly more effective than placebo in inducing the histologic response (Odds Ratio(OR) 37.81, 95% Confidence interval(CI) 14.98-85.64, p<0.00001). They were also more effective than the placebo in inducing a clinical response (OR 2.5).

The most frequently reported side effects were infections, which were mild and almost always tolerated without severe consequences. According to data derived from this meta-analysis, we conclude that topical steroids can be used reliably to reduce the inflammatory response in the esophagus and facilitate clinical and endoscopic improvement by inducing the remission of this condition.

Keywords: Esophageal Candidiasis; Eosinophils Per High Power Field; Fluticasone; Topical Steroids; Eosinophilic Esophagitis

1. Introduction

Eosinophilic esophagitis (EoE) represents a recurring inflammatory disease of the esophagus characterized by eosinophilic infiltration. The common symptoms associated with this condition include dysphagia, odynophagia, and

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reflux-like symptoms. Genetics, environmental factors, and immune disorders are some factors that explain the mechanism of evolution of eosinophilic esophagitis [1].

Being a disease of atopic etiology, topical corticosteroids are the mainstay for managing this condition. This aims to reduce the inflammation of the esophagus and improve clinical outcomes. Additional understanding is required to understand the exact medication dosage and how long treatment is necessary to induce long-lasting remission [1,2].

This meta-analysis examines the drug's efficacy compared to the placebo to obtain the best response at endoscopic, clinical, and histological levels. Here, there is a focus on the systematic cataloging of data yielded by randomized trials to elicit the most relevant and helpful information about the efficacy and safety of steroids in treating eosinophilic esophagitis.

2. Methods

2.1. Literature Search

The investigators collected the studies from various databases following a literature review. The searched databases include PubMed, EMBASE, Medline, ISI Web of Science, and the Cochrane Database of Systematic Reviews. The inclusion criteria, for example, involved searching for articles containing the Medical Subject Headings (MeSH) terms "eosinophilic esophagitis, topical steroids, and randomized controlled trials." Besides, the articles were scanned from the references and the referential review articles, and additional primary studies were searched for that would aid in determining eligibility. The robust research process entailed looking for a plethora of studies with a high level of relevance that provided the pooling meta-analysis process with legitimate and unbiased sources of information that were utilized as supportive evidence.

2.2. Study Selection

The meta-analysis included all randomized control trials (RCT) using topical steroids to treat EoE. The researchers took on the robust task of reviewing the titles, abstracts, and full-text papers of the studies to identify the ones that comply with the inclusion criteria. In the eventual case of any disputes or disagreements during the study selection process, the team acted as a decision-making body, achieving consensus through the discussion. The rigorous appraisal of the inclusion and exclusion of trials and their quality ensured that the eligible and high-quality trials were used to conduct the meta-analysis.

2.3. Outcome Measures

The primary outcomes of interest in this meta-analysis were:

- Histological response rate- <15 eosinophils per high-power field
- Clinical response rate: Swallowing problems or food impaction with the use of local steroid therapy vs placebo.
- Endoscopic response rate: This resulted in the measurement of the rate at which patients with endoscopic improvement, like a reduction in esophagus inflammation or strictures, were produced after applying topical steroids on patients and compared with that of the placebo.

The latter outcomes are clinically significant and are the pivotal aims of EoE treatment, during which symptoms are relieved, the mucosal rash is eliminated, and the re-occurrence of these symptoms is prevented.

2.4. Meta-Analysis

A meta-analysis was conducted using the RevMan 5.3.5 software, a well-evaluated tool for performing systematic reviews and meta-analyses. For dichotomous outcomes (histological, clinical, and endoscopic response rates), the research team determined odd ratios and 95% confidence intervals. To determine the heterogeneity among the studies included in the analysis, the researchers used the I2 statistic. By calculating I2 statistics, it is possible to measure the percentage of variations in results among studies caused by heterogeneity rather than random chance. I2 values equal to or less than 50% indicate low heterogeneity, while high values, like more significant than 75%, signify appreciable heterogeneity.

These analytic techniques helped to consolidate and structure the accessible evidence of topical steroid therapy used in EoE in a comprehensive report.

This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

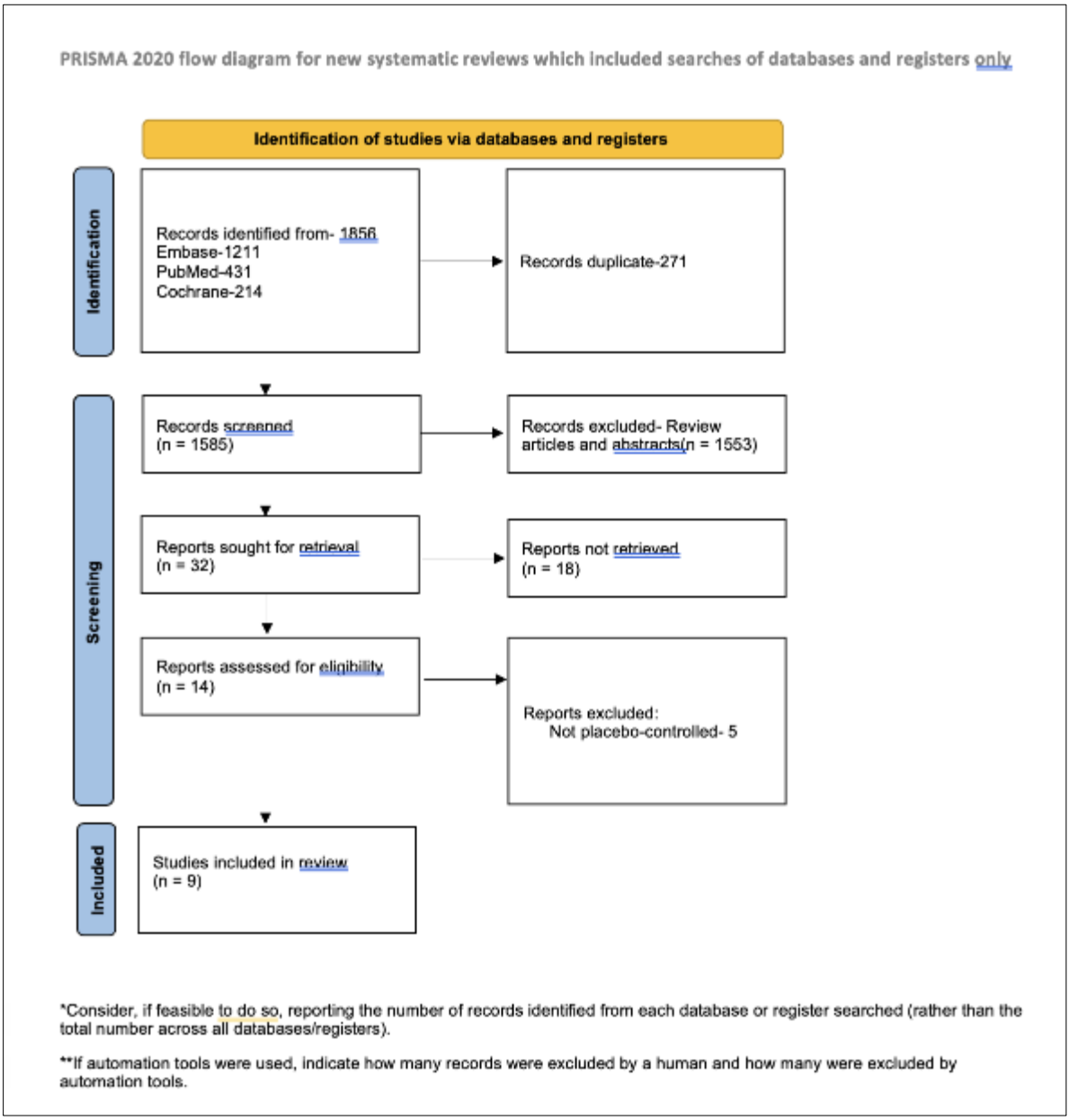

Figure 1 Prisma diagram

2.5. Data Extraction and Risk of Bias Assessment

All retrieved articles were imported into the Endnote 20 software, and duplicates were removed. Subsequently, two independent authors screened the titles and abstracts, reviewed the full texts, performed data extraction, and assessed the risk of bias. The following details were extracted: study identifier, publication date, recruitment period, trial registration number, study location, study design, baseline characteristics of the participants (sample size, mean age, proportion of males, mean BMI, smokers, alcohol drinkers), treatment regimen given (types and dosages of steroids/placebo), treatment duration, outcome measurement, and the treatment outcome.

According to the Cochrane's Risk of Bias (RoB) tool 2.0, a "high risk," "some concerns," or "low risk" of bias was considered. The RoB 2 tool assessed bias due to the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, bias in the selection of the

reported result, and the overall RoB. The reviewers would reconcile for any disagreement until a mutual agreement was achieved.

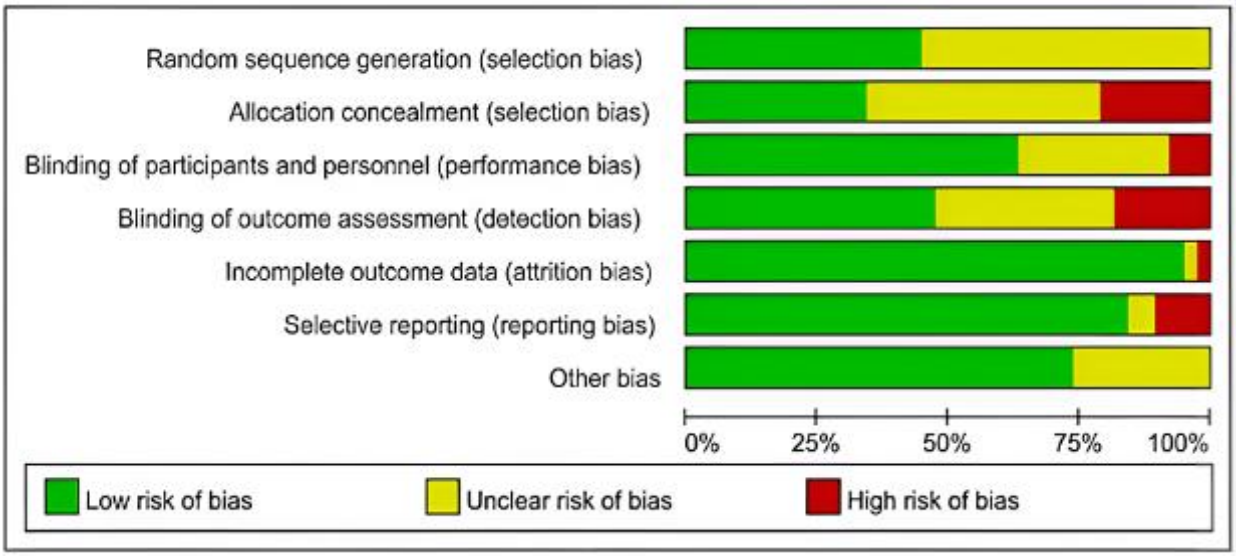

Figure 2 The risk of bias

2.6. Strengths and Limitations

The key strengths of this systematic review and meta-analysis include:

- Comprehensive literature search: The researchers used applicable MesH words and keywords and multiple databases to get all the relevant RCT studies, so there was little chance of relevant studies being omitted.
- Focus on RCTs: The review research focused only on RCTs, limiting internal inaccuracy and confounding. Thus, it helps increase the internal validity of the review
- Clinically relevant outcomes: Key outcomes (histological, clinical, and endoscopic response rates) of EoE management match the therapeutic objectives; thus, these indicators represent a direct contribution to the EoE patient's management.
- Robust meta-analytic methods: This approach of meta-analysis, which further can be based on sound, well-established meta-analytic techniques such as OR calculation and assessment of heterogeneity, offers dependable and easy-to-understand results.

Limitations of the Study

- Heterogeneity in study populations and interventions: While rigorous control trials are the primary focus, even with that, there may still be some patient variance, steroid formulations, or treatment protocol differences among the included studies that may alter the outcomes.
- Interpretation of clinical and endoscopic response: The researchers propose that the results are taken carefully considering the moderate to high levels of heterogeneity observed.
- Adverse events reporting: This meta-analysis might not cover all possible adverse effects of topical steroid therapy.

3. Results and Discussion

This study's evidence base included nine RCTs pooling 193 subjects (Figure 1). The key findings from the meta-analysis are as follows:

3.1. Histological Response Rate

The findings of this meta-analysis (Figure 3) revealed that steroids given topically were significantly more effective in eliciting histological responses in patients with eosinophilic esophagitis (EoE) compared to placebo. The study stipulates that the odds ratio (OR) for histological response was 37.81 (95% confidence interval [CI]: 14.98-85.64,

p<0.00001), meaning that per the treatment group given topical steroid patients were more likely to get histological remission/improvement than those in the placebo group. The heterogeneity among those studies that took part was low (i2 value of 0% and p=0.72). Therefore, the results were consistent with those of all those research studies.

Repeated treatment demonstrated that the efficacy of steroids is predictable for practical clinical purposes [3,4]. The data from this study is in line to other studies, where the efficiency of corticosteroids to reduce the symptoms and induce histological remission in the case of EoE patients was demonstrated. The study by the Centuro researchers established that long-term treatment is necessary for EoE [1]. While the disease has no permanent cure, it may require prolonged maintenance [5]. The present meta-analysis points to the crucial contribution of topical steroid treatment, which, together with a strict diet and administration of medications before food intake, should be considered a cornerstone for the multifaceted treatment of EoE.

Through reduced eosinophilic inflammation and restored tissue structure, topical steroids may deliver therapeutic effects suitable for preventing chronicity and disease worsening in EoE patients [6,7]. The observed consistent improvement of histologic results in this meta-analysis strengthens the argument for clinicians to use topical steroids for EoE patients as a first-line pharmacological intervention.

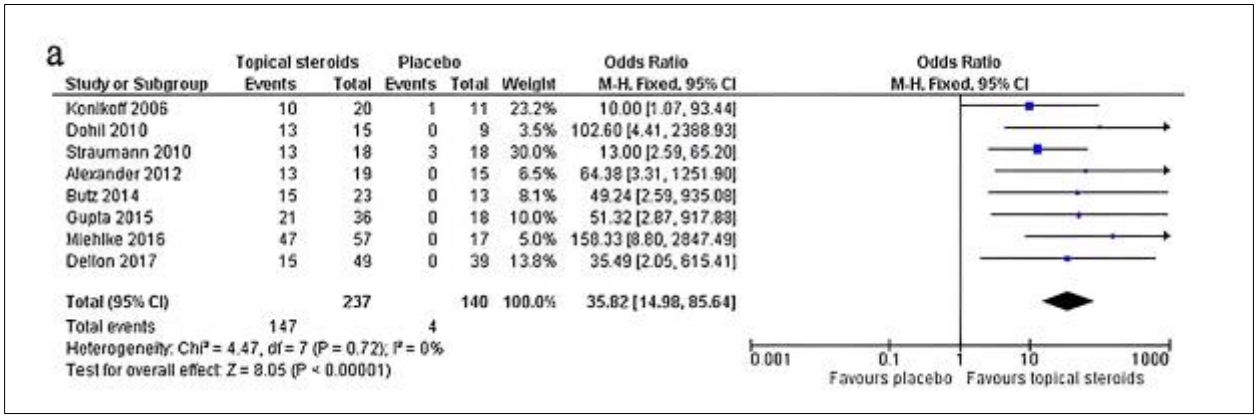

Figure 3 Forrest Plot for histologic response

3.2. Clinical Response Rate

The meta-analysis (Figure 4) also showed that the topical steroid treatment was much better than placebo since it led to clinically significant improvements in people with EoE. The OR for clinical response was 2.53 (p=0.02).

This result shows that patients with steroid treatment were 2.5 times more likely to show improvement in symptoms, including dysphagia, food impaction, and reflux-like symptoms, compared to those treated with a placebo. While the authors of the meta-analysis conclude that topical steroids have a clinical benefit, a moderate level of heterogeneity was found across the different included studies (i2=60%, p=0.02). This can be attributed to the variance of the effect of treatment on symptoms across different trials amongst participants.

The heterogeneity in clinical response could be attributed, among other reasons, to the differences in the assessment and reporting of clinical symptoms, the subject population, or treatment protocols in the assorted trials [8]. Unlike the moderate heterogeneity in the clinical response, the total observation implies that topical corticosteroid therapy positively affects EoE patients' clinical outcomes. The clinician must consider the impact of treatment, which may be enhanced or reduced based on the individual patient responses.

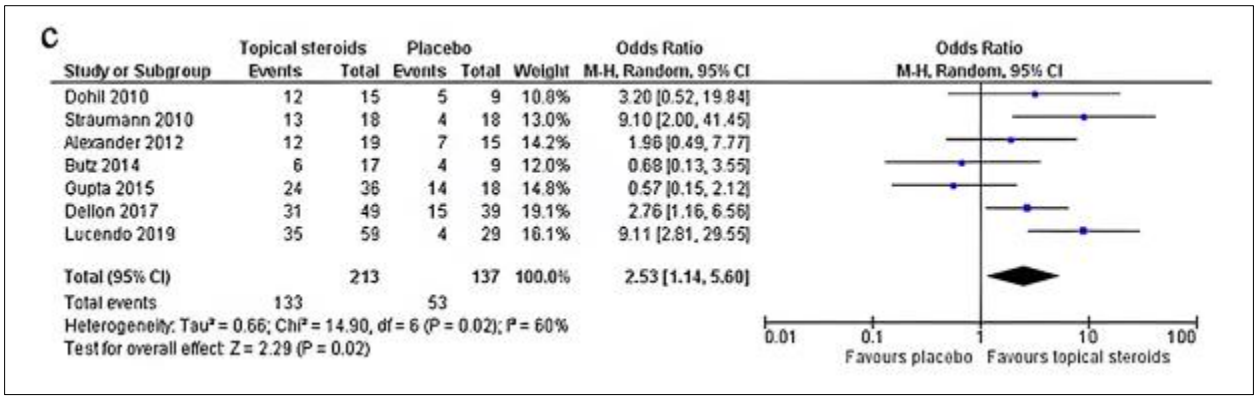

Figure 4 Forrest plot for clinical response

3.3. Endoscopic Response Rate

Topical steroids were superior to placebo in facilitating endoscopic response in patients with EoE (Figure 5). The OR for an endoscopic response was 3.51. The results suggest a significant link between patients using topical steroid therapy and showing endoscopic improvements in their condition (odds ratio 3.5, p=0.005); these patients were 3.5 times more likely to achieve endoscopic improvement than those receiving placebo. Homogeneity among the studies included in the meta-analysis was acceptable, as the I2 value was 0% (p = 0.57).

The endoscopic exam is a vital part of EoE management as it reveals the details of the structural and inflammatory transformations within the esophagus [9]. With topical steroid therapy, we can avert the complications related to EoE, like the occurrence of strictures and fibrotic transformations. The continued and considerable recovery and the sustained endoscopic response noted in the present meta-analysis strongly support the use of topical steroids administration. This evidential base implicates topical steroid therapy as a beneficial overall pharmacological measure in managing the endoscopic characteristics of EoE.

Hence, the meta-analysis conclusively demonstrates that the topical steroid therapy is more highly effective than the placebo in causing a histological, clinical, and endoscopic response in patients with EoE and the area under the curve for histological response (AHR), clinical response (ACR), and endoscopic response (AECR) was 0.86, 0.7. Although the statistics showed that the histological and endoscopic response results were identical among the investigated studies, they displayed moderate heterogeneity in the clinical results. The most common side effects were infections, usually well-tolerated by the participants.

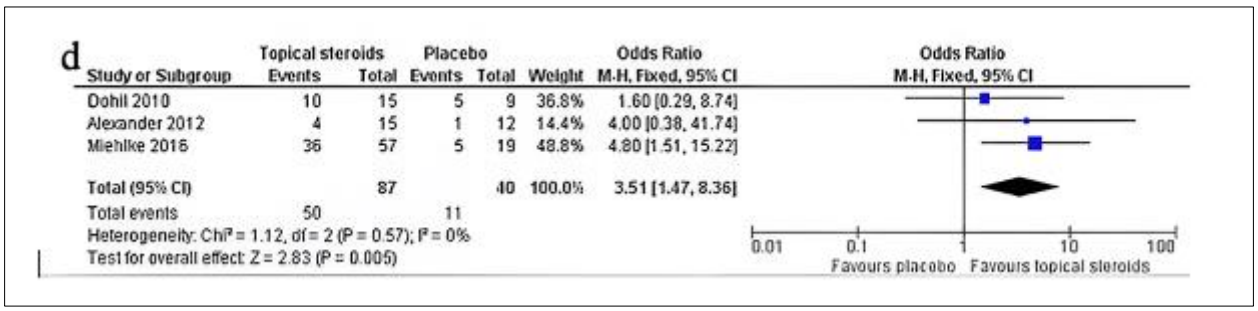

Figure 5 Forrest plot for endoscopic response

3.4. Adverse Events(AE)

Even though our meta-analysis had no data on the adverse events associated with topical steroid therapy in the treatment of EoE, it documented several clinical features that were reported in patients treated with steroids, such as esophageal candidiasis, facial flushing, headache, and sleep disorders. The meta-analysis does not present a complete profile of adverse events in the disorder that should be considered while evaluating the option. This is a significant restriction because clinical judgments and patient care management depend on considerable knowledge about treatments' safety and tolerance profiles.

The meta-analysis on AEs by Najjar et al. [4] shed new light on adverse events. The study reported that 86% of adverse events were defined using subjective, minimizing terms like "easily managed" or "well-tolerated," even though it was a different disease-specific area of research. This conclusion highly emphasized the need for an open and objective description of adverse effects.

4. Conclusion

After the meta-analysis, it is clear that topical corticosteroid therapy has a positive effect on Eosinophilic Esophagitis (EoE). Clinical trial outcomes demonstrate significant differences concerning the efficiency of topical steroid treatment compared to the placebo group. Meta-analysis showed that the probability of topical steroid therapy patients undergoing histological remission or improvements was up to 37-fold more significant than in placebo patients. Moreover, there was a 2.5-fold higher rate of patients experiencing improvement in the symptoms and a 3.5-fold higher rate of patients displaying endoscopic signs of success.

The considerable positive evaluation for histological and endoscopic results, as the small heterogeneity indicated, also provides confidence for topical steroid utilization in treating EoE. However, from the heterogeneity level, clinical responses were seen to have a moderate effect.

Compliance with ethical standards

Disclosure of conflict of interest

The authors do not have any disclosures.

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