Original Investigation

Efficacy of Photodynamic Therapy vs Other Interventions in Randomized Clinical Trials for the Treatment of Actinic Keratoses
A Systematic Review and Meta-analysis

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IMPORTANCE Photodynamic therapy (PDT) is used extensively to treat actinic keratoses (AKs). An analysis of the effectiveness of PDT compared with other treatments may help physicians decide what role it should play in their own clinical practices.

OBJECTIVE To determine the effectiveness of PDT for the treatment of AKs relative to other methods.

DATA SOURCES MEDLINE, EMBASE, Web of Knowledge, and Cochrane Central Register. No restrictions on years were placed, and all searches extended to the year of each database inception. Our search was conducted on March 20, 2013, and included the search terms solar keratosis, actinic keratosis, photodynamic therapy, and photochemotherapy. No restrictions were used for the search string.

STUDY SELECTION Only randomized PDT trials that used aminolevulinic acid hydrochloride or methyl aminolevulinate hydrochloride as stabilizers with 10 or more participants were considered. Two of the authors undertook the search independently.

DATA EXTRACTION AND SYNTHESIS Data were extracted independently by the 2 authors. We assessed data quality using the Jadad scoring system and used a random-effects model for pooled data analysis.

MAIN OUTCOMES AND MEASURES Primary outcome measures specified a priori were lesion response, cosmetic results, and patient satisfaction after the intervention.

RESULTS Our search identified 875 journal articles and meeting abstracts. We excluded 862 owing to lack of adherence to our inclusion criteria or lack of author response to our queries for further information. We assessed 13 studies for inclusion in our final synthesis, of which 4 were eligible for final meta-analysis. The only comparator for which meta-analysis was performed was cryotherapy. The meta-analysis consisted of 641 participants, with a total of 2174 AKs treated with cryotherapy and 2170 AKs treated with PDT. Compared with cryotherapy, the pooled relative risk for the meta-analysis for complete response (lesion clearance) was 1.14 (95% CI, 1.11-1.18) at 3 months after treatment. Visual inspection of a funnel plot revealed no publication bias, which was confirmed by the Begg test (P = .80).

CONCLUSIONS AND RELEVANCE Photodynamic therapy has a 14% better chance of complete lesion clearance at 3 months after treatment than cryotherapy for thin AKs on the face and scalp.

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Actinic keratoses (AKs) are rough, scaly cutaneous lesions typically found on the skin of fairly complected older individuals with heavy sun exposure. Actinic keratoses are widely recognized as lesions that have the potential for full transformation to cutaneous squamous cell carcinomas. Prevalence of these lesions in patients with lighter skin types is extremely high, with some studies finding more than 80% of some cohorts affected. Estimated transformation rates for AKs vary from 0.075% to 0.096% per lesion per year, yielding 10-year neoplastic transformation rates estimated at 10.2% to 20.0% for the average affected patient with 7.7 AKs.

Evidence that treatment of these lesions reduces incidence of cutaneous neoplasms is largely low level in nature, but treatment makes intuitive sense for most physicians. Many treatments exist for this purpose, including cryotherapy, topical chemotherapy and immunomodulators, laser ablation, and photodynamic therapy (PDT). Photodynamic therapy is an increasingly popular treatment with reported high rates of efficacy and claims of improved cosmetic outcomes. Results of multiple randomized clinical trials (RCTs) have now been published concerning PDT and other treatments, with varying outcomes. Thus, many clinicians are still uncertain which method is best for their patients.

We were interested in how treatment with PDT compares with traditional/alternative therapy for the outcome of lesion resolution, cosmetic satisfaction, and adverse events. We focused exclusively on the results of RCTs to reduce the chances of bias. Results of our analysis should help practicing clinicians choose treatments based on the best available evidence.

Methods

Registration, Databases, and Search Strategy
This review was registered with the University of York Centre for Reviews and Dissemination before completion (registration No. CRD42013004743; http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013004743#.U4i0UawBK). We systematically searched the MEDLINE, EMBASE, Web of Knowledge, and Cochrane Central Register databases. Search terms included solar keratosis, actinic keratosis (MeSH), photodynamic therapy, and photochemotherapy (MeSH). No restrictions were used for the search string. We performed our initial enquiry on March 20, 2013. The search was conducted by the University of California Davis Medical Center librarian, who uploaded the results into a citation database program for review (EndNote; http://endnote.com/).

Eligibility Criteria
Eligibility was restricted to studies with human participants only, a randomized study design, and at least 10 patients. Studies had to concern the efficacy of topical PDT compared with an alternative, non-PDT treatment. Any population, age, body location, or comparative treatment was allowed. All languages and abstract publications from scientific meetings were included to reduce the chances of publication bias. We examined titles and abstracts for relevant studies. To be included in the analysis, studies had to report lesion resolution as part of their outcome measures and/or cosmetic outcomes after PDT relative to an alternative treatment. The study population included any patient with a clinical and/or a histologic diagnosis of AK. Duration of follow-up was not a criterion. Restrictions were not placed on the type of PDT protocol used if the photosensitizer was topical aminolevulinic acid hydrochloride or methyl aminolevulinate hydrochloride, because these have been the mostly widely available in North America and Europe and thus most likely to be relevant to current physician practice.

Selection Process
Selection criteria were prespecified. Two of us (D.B.E. and G.P.) selected studies independently. Disparities in selection were resolved by discussion with the prior agreement that any unresolved conflict would be resolved by a third party (A.W.A.). We extracted and summarized the details of eligible trials on data collection forms and worked in concert to double check entered data. Effort was made to exclude duplicated data by comparing author lists, interventions, and cohort numbers. Authors were not blinded to the names of the trial authors, journals, or institutions. In situations where needed data were not reported, the investigators made attempts to correspond with study or abstract authors via e-mail.

Extracted Data and Outcomes of Interest
Primary outcome measures were lesion response, cosmetic results, and patient satisfaction after the intervention. Other data of interest included other outcome measures, characteristics of the study participants, treatment location, intervention details, duration of follow-up, lesion recurrence, adverse events or complications, study setting, number of participants and lesions treated, withdrawals, study analysis type (intention to treat vs per protocol), blinding, follow-up time, split patient method vs separate arms allocation, patient demographics, comorbid conditions such as immunosuppression, study methods, reported statistical analysis, and lesion grade.

Assessment of Bias Risk
We used the Jadad score to assess the methodologic quality of each RCT independently. Each investigator performed the analysis separately with the predetermined agreement that unresolved conflicts would be decided via a third party. Publication bias was assessed using visual inspection of a funnel plot of the study size vs standard error, with formal statistical testing using the Begg adjusted rank correlation test and fail-safe number.

Statistical Analysis
Meta-analysis was performed on those studies that had the same follow-up period and efficacy outcome. The relative risk ratios were identified based on the publication results. The inverse variance method was then used to calculate the pooled relative risk using random-effects modeling. All analyses were performed using commercially available software (STATA, version 11.2; StatasCorp).
Results

Study Screening
Our search of the MEDLINE, EMBASE, Web of Knowledge, and Cochrane Central Register databases identified 875 publications and meeting abstracts. We then excluded 90 duplicates (Figure 1). We excluded 764 after review of abstracts demonstrated clear lack of adherence to our inclusion criteria. Three meeting abstracts were eliminated after attempts to contact authors to procure outcome data were unsuccessful. These abstracts concerned PDT and the comparators imiquimod and sequential fluorouracil. A total of 13 studies were selected for final inclusion in the review.

Study and Participant Characteristics
Four different modalities (cryotherapy, fluorouracil, imiquimod, and carbon dioxide [CO2] laser) were identified in comparison with PDT. Except for 2 studies from the United States, most were conducted in international settings. Five of the 13 studies were conducted at multicenter sites. Follow-up ranged from 4 weeks to 12 months. Often type of data analysis (intention to treat vs per protocol) was not specified. Of studies where it was specified, per protocol appeared to be the most common analysis performed (Table 1).

Most study participants were older and tended to favor male enrollment. Mean age of participants in these comparative trials ranged from 59.4 to 75.8 years with the fraction of male participants ranging from 47% to 100%. Race was inconsistently reported, with many trials listing no information or Fitzpatrick skin type. When this information was reported, participants were primarily white or characterized as having lighter Fitzpatrick skin types. Attrition ranged from 1.7% to 22.8%. Locations included the face and/or scalp in 9 studies, extremities and head and neck in 1 study, face in 1 study, and forearms and hands in 2 studies (Table 2).

Table 1. Characteristics of Studies Meeting Search Inclusion Criteria by Comparison Treatment

<table>
<thead>
<tr>
<th>Source</th>
<th>Multicenter</th>
<th>Split Study</th>
<th>No. of Patients</th>
<th>Age, y</th>
<th>No. (%)</th>
<th>Analysis Used</th>
<th>Length of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male Sex</td>
<td>Dropout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szeimies et al, 2002</td>
<td>Yes</td>
<td>No</td>
<td>202</td>
<td>71.5 (42-89)</td>
<td>124 (61.4)</td>
<td>PPb</td>
<td>3 mo</td>
</tr>
<tr>
<td>Freeman et al, 2003</td>
<td>NR</td>
<td>No</td>
<td>204</td>
<td>64 (33-89)</td>
<td>119 (58.3)</td>
<td>ITT safety; PP efficacy</td>
<td>3 mo</td>
</tr>
<tr>
<td>Morton et al, 2006</td>
<td>Yes</td>
<td>Yes</td>
<td>119</td>
<td>74.8 (53.9-93.3)</td>
<td>108 (90.8)</td>
<td>0</td>
<td>ITT and PP</td>
</tr>
<tr>
<td>Kaufmann et al, 2008</td>
<td>Yes</td>
<td>Yes</td>
<td>121</td>
<td>68.9 (38-89)</td>
<td>78 (64.5)</td>
<td>2 (1.7)</td>
<td>ITT and PP</td>
</tr>
<tr>
<td>Hauschild et al, 2009</td>
<td>Yes</td>
<td>No</td>
<td>346</td>
<td>70.5 (41-94)</td>
<td>248 (71.7)</td>
<td>48 (13.9)</td>
<td>PP</td>
</tr>
<tr>
<td>Szeimies et al, 2010c</td>
<td>Yes</td>
<td>No</td>
<td>284</td>
<td>70.5 (41-94)</td>
<td>248 (87.3)</td>
<td>16 (5.6)</td>
<td>ITT and PP</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kurwa et al, 1999</td>
<td>NR</td>
<td>Yes</td>
<td>17</td>
<td>NR (53-79)</td>
<td>8 (47.1)</td>
<td>PPb</td>
<td>6 mo</td>
</tr>
<tr>
<td>Smith et al, 2003</td>
<td>NR</td>
<td>No</td>
<td>36</td>
<td>61.4 (NR)</td>
<td>29 (80.6)</td>
<td>1 (2.8)</td>
<td>PP</td>
</tr>
<tr>
<td>Imiquimod</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Sotiriou et al, 2009</td>
<td>NR</td>
<td>Yes</td>
<td>30</td>
<td>59.4 (46-71)</td>
<td>25 (83.3)</td>
<td>PPb</td>
<td>6 mo</td>
</tr>
<tr>
<td>Serra-Guillén et al, 2011</td>
<td>No</td>
<td>No</td>
<td>58</td>
<td>73.3</td>
<td>52 (89.7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Hadley et al, 2012</td>
<td>No</td>
<td>Yes</td>
<td>61</td>
<td>75.8 (55-90)</td>
<td>61 (100.0)</td>
<td>11 (18.0)</td>
<td>PPb</td>
</tr>
<tr>
<td>Serra-Guillén et al, 2012</td>
<td>No</td>
<td>No</td>
<td>136</td>
<td>73.3 (NR)</td>
<td>92 (67.6)</td>
<td>31 (22.8)</td>
<td>PPb</td>
</tr>
<tr>
<td>CO2 Laser</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Scola et al, 2012</td>
<td>No</td>
<td>Yes</td>
<td>21</td>
<td>73.7 (55-84)</td>
<td>19 (90.5)</td>
<td>1 (4.8)</td>
<td>ITTb</td>
</tr>
</tbody>
</table>

Abbreviations: CO2, carbon dioxide; ITT, intention to treat; NR, not reported; PP, per protocol.

b Assumed analysis per description of methods.

Assumed analysis per description of methods.
Interventions
Photodynamic therapy and comparative treatment protocols were heterogeneous (Table 2). For PDT protocols, 9 studies\(^\text{14-17,20,23,25,26,28}\) used some form of curettage or scraping before sensitizer application; the remainder used no preparation or did not report it. Seven interventions\(^\text{18,21,22,25,26,28,40}\) used aminolevulinic acid photosensitizers, including 2 patch aminolevulinic acid, and the rest\(^\text{14-17,20,23}\) used methyl aminolevulinate. Incubation time varied from 1 to 4 hours. Light source wavelength ranged from 417 to 740 nm (blue to red). Photodynamic therapy sessions ranged from 1 to 2; 2-session interventions had variable intersession durations.

For comparative interventions, no pretreatment was usually performed. Cryotherapy treatments ranged from 1 to 2 freeze-thaw cycles, with some studies\(^\text{16,17}\) repeating treatment at various intervals if unresolved. Some studies reported freeze times\(^\text{14,18,40}\); others did not report specific treatment variables. Topical treatments, fluorouracil, and imiquimod were used at various frequencies and durations.

Study Quality
The 13 identified studies received a Jadad score ranging from 1 to 3 (scores of 0-3 indicating poor methodologic quality; 4-5, good methodologic quality).\(^\text{45}\) None of the RCTs described randomization methods, and no RCT was double-blinded in this review. Except for 2 studies,\(^\text{14,23}\) all provided a description of an account of all patients (Figure 2 and eTable 1 in the Supplement).
Efficacy of PDT vs Other Interventions for AKs

Outcomes

AK Clearance

The primary outcome measures for 12 of the 13 studies were clearance rate of treated AKs, number of treated patients with at least 75% clearance of AKs, and number of patients achieving total clearance of all AKs. The remaining study only assessed treatment tolerability and patient satisfaction and did not report efficacy of lesion clearance.

Of the 6 articles examining PDT vs cryotherapy, 2 studies reported lesional complete clearance rates that significantly favored PDT vs cryotherapy at 12 weeks and at 1 year on the face and scalp (with long-term data from a previously reported study) (Table 3). One study reported no significant difference between cryotherapy and PDT at 24 weeks on the extremities. Two studies reported no significant differences in lesion response, but the sequential use of both methods resulted in the statistically significant higher response rate.

In the 2 studies comparing fluorouracil and PDT, Kurwa et al found that the mean lesional area diminished a similar amount in PDT- and fluorouracil-treated areas at 6 months after treatment, and Smith et al found that at 1 month after treatment with PDT or fluorouracil, both treatment arms had similar efficacy. The study by Smith et al also had a third arm that included PDT with a pulsed-dye laser light source, but only 8% of patients were found to have 100% clearance of treated lesions.

For 4 studies looking at outcomes of PDT vs imiquimod, only 3 reported outcomes in terms of complete clearance rate of AK lesions, and the remaining study was concerned solely with tolerance and satisfaction. Of the 3 studies evaluating lesion response, only Hadley et al reported the mean AK clearance rate for their study, which significantly favored PDT at their 1-month assessment time. Sotiriou and colleagues found that response rates obtained in grade 1 lesions (mild/thin slightly palpable AK, better felt than seen) were higher for both treatments than for thicker lesions, but at 6 months no significant difference in cure rate was found between the treatment groups. Serra-Guillén et al also found no statistical difference between imiquimod and PDT in lesion response, but the sequential use of both methods resulted in the statistically significant higher response rate.

Last, Scola and colleagues compared PDT and the CO2 laser. These investigators found significantly greater median AK lesion reduction on the PDT-treated side than on the CO2 laser-treated side.

Cosmetic Outcomes

Cosmetic outcomes and patient satisfaction were described for the 6 studies comparing PDT and cryotherapy and the 4 PDT vs imiquimod studies. In the 5 studies providing the investigators’ cosmetic assessments, only 2 found a statistically significant difference favoring PDT compared with cryotherapy (Table 3). In the 8 studies providing the patients’ cosmetic assessment, satisfaction, and preference, PDT was the predominately favored treatment modality over cryotherapy and topical imiquimod.
Adverse Events
Detailed reporting of adverse events were available for PDT, cryotherapy, and imiquimod (eTable 2 in the Supplement). Adverse events were common for PDT in every study (to 100%) where they were reported but were mostly minor in nature. Photosensitivity, pain, erythema, and pruritus accounted for most events. Cryotherapy also induced pain and pruritus, but at rates less than those for PDT. One of the few complication frequencies to exceed that for PDT was the incidence of hypopigmentation, which was noted in 33% of the cryotherapy group vs 9% of the PDT group in one study.20 For imiquimod, local skin reaction was noted at 93% in one study26 and moderate or intense in nature in 76% of another trial.23 Regarding erythema resulting from PDT and fluorouracil, Kurwa et al25 noted it was more prevalent in the PDT arm 1 week after treatment inception, equal to that of the PDT arm 2 weeks after, and more prevalent than that of the PDT arm 3 weeks after starting. Also of note, 2 patients in their study dropped out of the fluorouracil arm because of severe erythema. Adverse events were not specifically reported for the CO2 laser vs PDT.28

Meta-analysis
Four trials were selected for meta-analysis regarding effectiveness outcomes of PDT vs cryotherapy.14-16,18 The other cryotherapy studies were excluded owing to incompatible follow-up times.17,48 We judged the other treatment methods (imiquimod, fluorouracil, and CO2 laser) ineligible for meta-analysis owing to different outcomes measures and follow-up times (imiquimod and fluorouracil) and lack of a comparator (CO2 laser).

With the 4 PDT vs cryotherapy studies, the pooled study population for the meta-analysis consisted of 641 participants, with a total of 2174 AKs treated with cryotherapy and 2170 AKs treated with PDT. Compared with cryotherapy, the pooled relative risk for the meta-analysis for complete lesion response was 1.14 (95% CI, 1.11-1.18) for PDT. That is, PDT has a 14% greater likelihood of achieving complete lesion clearance than cryotherapy at 3 months after treatment. Visual inspection of a funnel plot revealed no publication bias, which was confirmed by the Begg adjusted rank correlation test (P = .80). A fail-safe number was calculated at 29.

Discussion
Effectiveness Outcomes
Findings from our meta-analysis suggest a significantly larger treatment effect for PDT when used on thin (grade 1) AKs than for cryotherapy (OR, 1.86) on the face and scalp 12 weeks after treatment. Only a single study17 in our meta-analysis found cryotherapy to have higher efficacy rates than PDT. In that study, more than 60% of lesions were grade 2 (moderately thick AK, easily felt) or 3 (very thick and/or obvious AK). The other studies excluded thicker lesions or favored thinner ones. At least 1 trial20 suggests PDT is less efficacious when used for thicker AKs than for thinner ones. Results regarding treatment options for AKs in locations other than face and scalp were not addressable within our meta-analysis. However, in their RCT, Kaufmann et al27 found that cryotherapy administered as a double freeze-thaw cycle was significantly more efficacious than PDT (88% vs 78% complete clearance) when used on the extremities, although patients preferred PDT treatment. This finding may reflect the fact that cryotherapy efficacy increases with increasing freeze times, but so too do complications.30

Cosmetic and Patient Satisfaction Outcomes
Cosmetic outcomes and especially patient preference largely favored PDT. However, the investigators’ cosmetic outcome assessments were unblinded, leaving open the possibility of bias. Nonetheless, multiple clinical trials have reported improved cosmesis after PDT, specifically improvements in lentigines, skin roughness, fine lines, and sallow complexion.31-36 The cosmetic benefits of PDT may explain the patient preference and satisfaction of PDT compared with a physically destructive method, such as cryotherapy.

Fluorouracil has also been demonstrated to improve cosmetic appearances in patients.38,39 However, the included trials21,25 did not report results regarding cosmetic outcomes or patient preferences. The only study comparing PDT and the CO2 laser28 did not define their cosmetic and patient outcomes; therefore, their data could not be assessed adequately.

Quality of the Evidence
Although all the considered trials were randomized and controlled, they were of lower quality, with Jadad scores of 1 or 2. The primary deficits in quality were the lack of double-blind design and description of randomization methods. However, no sources of bias were evident in our funnel figure or heterogeneity test. Future investigators should report study methods more clearly to improve study quality assessments.

Clinical Implications/Applicability of Evidence
Our meta-analysis investigated outcomes of treatment predominantly on the face and scalp, the location of most of the AKs in most patient populations. Thus, our results are highly relevant to practicing physicians. Photodynamic therapy is an effective treatment with excellent cosmetic outcome and appears to be more effective than the commonly used cryosurgery on the face and scalp. Treatment recommendations need to be tailored toward particular patient circumstances. Those patients with a limited number of lesions and low cosmetic concerns might prefer cryotherapy, which typically does not require a separate treatment visit. Those patients with multiple lesions and concern regarding cosmesis might be better treated with PDT, given its higher efficacy.

Many of the studies used methyl aminolevulinate, a topical sensitizer used commonly in Europe but recently withdrawn from the market in the United States. However, studies suggest efficacy of aminolevulinic acid and methyl aminolevulinate to be similar.46

Strengths and Limitations
Strengths of this study include the relatively similar treatment locations and large numbers of patients included. Limi-
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Comparisons With Previous Reviews
Fayter et al performed an exhaustive systematic review on numerous applications of PDT, including the treatment of AKs. They performed a meta-analysis regarding PDT vs cryosurgery and found no difference in treatment effects between the two. Their analysis included a trial that was not identified in our search. That study compared methyl aminolevulinate-sensitized PDT with an intervention at the discretion of the treating physician. They further included data from the 12- and 24-week follow-ups after finding the outcomes were similar. This difference may explain the discrepancy of their meta-analysis results with our own results. Gupta et al published a Cochrane review on the treatment of AKs in late 2012. Their systematic review concluded that aminolevulinic acid-sensitized PDT was superior to cryosurgery based on the results of a single study. They did not perform a meta-analysis for methyl aminolevulinate-sensitized PDT, because they believed too much heterogeneity existed in the study results.

Comparisons With Previous Reviews

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Conclusions
For thin AKs on the face or scalp, PDT has a 14% better chance of lesion clearance compared with cryosurgery. Although not studied via meta-analysis, cosmetic outcomes after PDT were uniformly positive. Data regarding other comparators such as imiquimod, fluorouracil, and fractionated CO2 laser were more limited and prevented inclusion in our meta-analysis. Given that all of the studies included in our meta-analysis and in the cosmetic evaluations were unblinded, bias cannot be excluded.

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Author Contributions: Drs Patel and Armstrong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: All authors.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Patel, Armstrong.
Administrative, technical, or material support: Patel.
Study supervision: All authors.
Conflict of Interest Disclosures: None reported.

REFERENCES

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