Critical appraisal of bepotastine in the treatment of ocular itching associated with allergic conjunctivitis

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Abstract: Bepotastine besilate 1.5% solution is an H1-antihistamine recently approved by the Food and Drug Administration for the topical treatment of ocular itching associated with allergic conjunctivitis. Several clinical studies have demonstrated its safety as well as its efficacy versus placebo. This review finds that bepotastine besilate 1.5% solution is a suitable alternative to other agents within the class of H1-antihistamines, but there are no clinical trial data to suggest that it holds any specific advantages over other agents.

Keywords: allergic conjunctivitis, antihistamine, ocular itching

Introduction
Ocular itching associated with allergic conjunctivitis is a common patient complaint, and up to 40% of the US population is affected by allergic conjunctivitis, according to epidemiologic surveys.1 Although there are masqueraders of allergic conjunctivitis, including bacterial etiologies that produce the common papillary conjunctival reaction, diagnosis is generally straightforward. Typical exam findings, including conjunctival injection and papillae, combined with standard complaints of seasonal- or exposure-related ocular itching, lead to the clinical diagnosis. The disease begins with antigen exposure, which stimulates mast-cell degranulation, histamine release, and stimulation of a downstream inflammatory cascade.2 Management of the condition depends on several considerations. First, an oral agent may be used when allergic rhinitis or another systemic symptom is also present. Even in this case, however, eye drops may be necessary to control the ocular itching, despite systemic therapy. Second, there are a number of ophthalmic drugs available, with different mechanisms of action, dosing frequency, and tolerability. Finally, there is a wide range in price points for the various eye drops, including on-patent and generic formulations as well as prescription and over-the-counter alternatives.

Available oral H1-antihistamines include fexofenadine (Allegra® and Allegra-D®, prescription [Rx] only), loratidine (Claritin® and others, over-the-counter [OTC]), desloratidine (Clarinex®, Rx only), and cetirizine (Zyrtec®, OTC).3 Ophthalmic preparations, which tend to have a more rapid onset than oral agents with respect to ocular itching,2 include a number of drugs with antihistamine activity (H1-antagonists) and varying degrees of mast-cell stabilizing activity. These preparations include azelastine (Optivar®, Rx only), epinastine (Elestat®, Rx only), ketotifen (Alaway®, Zaditor®, and others, OTC), and olopatadine (Patanol®, Pataday®, Rx only) (see Table 1).4 Older agents that act primarily as mast-cell stabilizers are also available, including cromolyn (Crolom®, Opticrom®, Rx only),
Table 1 Classes of ophthalmic agents to treat allergic conjunctivitis. Adapted with permission from PDR for Ophthalmic Medicines, 37th edition, 2009

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Product name(s)</th>
<th>Class</th>
<th>Doses/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azelastine HCl</td>
<td>Optivar, generic</td>
<td>H1-antagonist/mast-cell inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Bepotastine besilate</td>
<td>Bepreve</td>
<td>H1-antagonist/mast-cell inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>Crolom, generic</td>
<td>Mast-cell inhibitor</td>
<td>4–6</td>
</tr>
<tr>
<td>Emedastine difumarate</td>
<td>Emadine</td>
<td>H1-antagonist</td>
<td>4</td>
</tr>
<tr>
<td>Epinastine HCl</td>
<td>Elestat</td>
<td>H1- and H2-antagonist/mast-cell inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Ketorolac tromethamine</td>
<td>Acular, Acular LS, Acular PF</td>
<td>Nonsteroidal anti-inflammatory drug</td>
<td>4</td>
</tr>
<tr>
<td>Ketotifen fumarate</td>
<td>Alaway, Zaditor</td>
<td>H1-antagonist/mast-cell inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Levocabastine HCl</td>
<td>Livostin</td>
<td>H1-antagonist</td>
<td>4</td>
</tr>
<tr>
<td>Lodoxamide tromethamine</td>
<td>Alomide</td>
<td>Mast-cell inhibitor</td>
<td>4</td>
</tr>
<tr>
<td>Loteprednol etabonate</td>
<td>Alrex, Lotemax</td>
<td>Corticosteroid</td>
<td>4</td>
</tr>
<tr>
<td>Naphazoline/antazoline</td>
<td>Vasocon-A</td>
<td>Antihistamine/decongestant</td>
<td>4</td>
</tr>
<tr>
<td>Naphazoline/pheniramine</td>
<td>Naphcon-A, Opcon-A, Visine-A</td>
<td>Antihistamine/decongestant</td>
<td>4</td>
</tr>
<tr>
<td>Nedocromil sodium</td>
<td>Alocril</td>
<td>H1-Antagonist/mast-cell inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Olopatadine HCl 0.1%</td>
<td>Patanol</td>
<td>H1-Antagonist/mast-cell inhibitor</td>
<td>2</td>
</tr>
<tr>
<td>Olopatadine HCl 0.2%</td>
<td>Pataday</td>
<td>H1-Antagonist/mast-cell inhibitor</td>
<td>1</td>
</tr>
<tr>
<td>Pemirolast potassium</td>
<td>Alamast</td>
<td>Mast-cell inhibitor</td>
<td>4</td>
</tr>
</tbody>
</table>

Bepotastine besilate 1.5% (Bepreve®, ISTA Pharmaceuticals, Rx only) is an H1-antihistamine that was recently granted FDA approval as a new treatment for itching associated with allergic conjunctivitis. This drug was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. and prepared as an oral medication for allergic rhinitis, receiving approval in Japan in July 2000. Development of the ophthalmic solution for US release was by ISTA Pharmaceuticals, and approval was granted in 2009 based on data from Japanese development programs as well as two domestic conjunctival allergen challenge studies, including a single-site Phase II/III trial and a multisite Phase III study. Available data concerning the pharmacology, clinical use, and safety of this drug will be reviewed.

In addition to antihistamines and mast-cell stabilizing drugs, various ophthalmic corticosteroids are available for the treatment of allergic conjunctivitis. Their use is typically limited to severe disease due to their more impressive side effect profile, which generally includes cataract formation and elevation of intraocular pressure. One specific drug in this class deserves special mention. Loteprednol etabonate 0.2% suspension is a topical ester corticosteroid that has been found to exhibit a low risk of intraocular pressure elevation over 4 weeks of therapy while reducing the symptoms of seasonal allergic conjunctivitis over a similar period of follow-up. Due to the combination of effectiveness and a low side effect profile, loteprednol may become a useful alternative to antihistamine therapy even in mild to moderate allergic conjunctivitis, especially when prescribed as a short-term course. Other, more potent corticosteroids, such as prednisolone acetate 1% solution, will likely remain in use for more severe disease.

Bepotastine besilate 1.5% ophthalmic solution (Bepreve, Rx only) is an H1-antihistamine that was recently granted FDA approval as a new treatment for itching associated with allergic conjunctivitis. This drug was originally developed in Japan by Ube Industries, Ltd. and Tanabe Seiyaku Co., Ltd. and prepared as an oral medication for allergic rhinitis, receiving approval in Japan in July 2000. Development of the ophthalmic solution for US release was by ISTA Pharmaceuticals, and approval was granted in 2009 based on data from Japanese development programs as well as two domestic conjunctival allergen challenge studies, including a single-site Phase II/III trial and a multisite Phase III study. Available data concerning the pharmacology, clinical use, and safety of this drug will be reviewed.

**Review of pharmacology, mode of action, and pharmacokinetics**

Bepreve, produced by ISTA Pharmaceuticals, is a clear, colorless to pale yellow solution containing bepotastine besilate as the active ingredient in a 1.5% solution, with a pH of 6.8 and osmolality of 290 mOsm/kg. This solution also contains benzalkonium chloride 0.005% as a preservative.

Bepotastine is an H1-antihistamine and an inhibitor of histamine release from mast cells. It is a piperidine derivative, similar to fexofenadine, ebastine, and loratidine. Multiple anti-inflammatory effects have been demonstrated, possibly as downstream mediators of the antihistamine activity. For example, in vitro studies suggest that bepotastine specifically suppresses proinflammatory cytokine production by keratinocytes, including inhibition of CD54 expression. Recent work on guinea pigs showed that bepotastine, along with several other H1-antihistamines, reduces vascular hyperpermeability in both antigen-induced and histamine-induced hyperpermeability models. This work also showed that bepotastine inhibits in vitro eosinophil chemotaxis induced by leukotriene B4, and pretreatment with bepotastine limits conjunctival eosinophil infiltration after topical platelet-activating factor instillation.

The pharmacokinetic properties of bepotastine as an ophthalmic solution are described in Phase I trial data from Japan.
and these will be described as reported in the FDA Office of Clinical Pharmacology review of the Japanese data. First, a repeated instillation study was performed, testing four-times-a-day dosing in both eyes for 7 days in 12 healthy adult male subjects, half of whom instilled bepotastine besilate 1.0% and half instilled the 1.5% formulation. Venous blood samples were measured by high-performance liquid chromatography and demonstrated a bepotastine plasma concentration peak 1–2 hours postinstillation. The mean maximum concentration (Cmax) for the 1.5% group was 7.3 ± 1.9 ng/mL, which was much lower than the Cmax seen in the Phase I single oral dose trial, even at the lowest tested oral dose (Cmax was 22.4 ± 2.1 ng/mL for the 2.5 mg oral dose). At the clinically relevant, approved Japanese oral dose of 10 mg, the Cmax was 101.3 ± 3.5 ng/mL, which is over 13 times higher than the Cmax seen in the repeated ophthalmic dosing trial. Thus, although there is systemic absorption of the ophthalmic drop, the plasma concentrations are quite low, minimizing the likelihood of systemic adverse effects. Furthermore, plasma concentrations at 24 hours postinstallation were below the quantifiable limit of 2 ng/mL in 11 of 12 subjects. In the oral single-dose study, 75%–90% of the administered dose was secreted in the urine as unchanged drug by 24 hours after administration within the 2.5–40 mg dose range.

An additional Phase I study addressed the metabolism of bepotastine by liver microsomes, showing that there was minimal metabolism by CYP3A4, CYP2C9, and CYP2C19, again as reported in English by the FDA Office of Clinical Pharmacology review of the Japanese data. Within the relevant concentration range, it was concluded that bepotastine would likely have no effects on concomitantly metabolized drugs involving these enzymes. Finally, a protein-binding Phase I study was performed, demonstrating 55.4% mean plasma protein binding of the drug 1–2 hours after a 10 mg oral dose. This binding level was independent of plasma drug concentration.

**Efficacy studies**

There have been two randomized, double-masked, placebo-controlled trials of bepotastine besilate ophthalmic solution as a treatment for ocular itching associated with allergic conjunctivitis. Both studies evaluated the effectiveness of the drug in comparison with its vehicle in a conjunctival allergen challenge (CAC) model. No comparative human clinical studies against other drugs have been performed, although bepotastine performed well compared with other H₁-antihistamines in an experimental model of allergic conjunctivitis in guinea pigs.

The CAC model employed was consistent between the two studies. Subjects were included on the basis of age (≥10 years) and a positive skin-test reaction to an allergen within the prior 2 years. Further, during two screening visits, subjects had to demonstrate a positive reaction to the testing protocol with respect to ocular itching and conjunctival redness. Visit 1 (day-21) was used to determine the lowest dose of the defined antigen (from skin testing for that patient) that would elicit an ocular allergic response. Visit 2 (day-14) was dedicated to confirming this consistent allergic response. The primary outcome variables measured were subject-evaluated ocular itching at 3, 5, and 7 minutes post-CAC (0–4 scale allowing half steps) and investigator-evaluated conjunctival redness at 7, 15, and 20 minutes post-CAC (0–4 scale allowing only whole steps).

Patients with validated responses to the CAC continued with the study protocol. At visit 3A (day 0), patients were randomly assigned to bepotastine besilate 1.0% ophthalmic solution, bepotastine 1.5%, or inactive vehicle (placebo), and one drop of the appropriate solution was instilled in each eye. Subjects returned 16 hours later (visit 3B) for a CAC. This time period was chosen to correspond to a duration of action suitable for once-daily dosing. Primary as well as secondary outcome measures were obtained at stated intervals, with grading of allergic conjunctivitis over the next 20 minutes. Monitoring for adverse effects was also employed.

Visit 4 (day 14) was scheduled to give a 2-week washout of the study drug instilled on day 0. At this visit, the appropriate drug was again instilled, and a CAC was administered after 8 hours and its effects graded. This time period was chosen to correspond with a suitable duration of action for a drug intended to be dosed twice daily. Visit 5 (day 28) was identical to visit 4, except CAC was administered at 15 minutes after the drug instillation. This interval was chosen to evaluate for a rapid onset of drug activity.

The first study was a Phase II/III single-center CAC study that analyzed 107 subjects evenly divided among the three study groups. Analysis of the primary outcomes, ocular itching, and conjunctival redness was applied to the per-protocol (PP) population that excluded protocol violators and to the intention-to-treat (ITT) population using last observation carried forward (LOCF) for missing data. Clinical significance was defined in the protocol as ≥0.5-unit between-group (placebo versus drug) difference between mean ocular itching or conjunctival redness at two of three time points at a study visit, and ≥0.5-unit mean difference at all time points. Statistical analysis of the conjunctival hyperemia data showed statistically significant...
improvements in hyperemia scores for both concentrations of drug compared with placebo (0.2–0.8 U difference, depending on time point, for bepotastine 1% versus placebo; −0.1–0.6 U difference for bepotastine 1.5%), but these improvements did not meet the predefined criteria for clinical significance. Ocular itching data, however, showed statistically and clinically significant improvements with both concentrations of bepotastine for the 15-minute (rapid onset of action) and 8-hour (twice-a-day dosing) CAC. Bepotastine 1.5% showed a similar effect at both of these time points (1.2–1.5 U for the 15-minute CAC, 1.2–1.7 U for the 8-hour CAC), but bepotastine 1.0% showed a dropoff in the effect with the longer duration (1.3–1.4 U for the 15-minute CAC, 0.9–1.1 U for the 8-hour test). Bepotastine 1.5% also demonstrated a significant effect in clinical significance for the 16-hour CAC (0.9–1.0 U).

The second efficacy study was a Phase III multicenter, prospective, double-masked, placebo-controlled, CAC clinical trial. The study enrolled 130 subjects at five clinical sites, dividing the subjects equitably between the three groups. Study methodology was identical to the single-center trial, except ocular comfort was graded by the subject on a 4-point scale immediately after drop instillation and 5 minutes later. In this study, both concentrations of bepotastine demonstrated at least a 1.2-unit reduction in ocular itching for the 15-minute and 8-hour CACs. Efficacy was significantly reduced for both concentrations at the 16-hour time point. A modest reduction in conjunctival redness was also seen, but only during the 15-minute CAC. There appears to have been a small decrease in ocular comfort for each drug concentration compared with placebo, although the measure approaches zero for all subjects at all time points, indicating relatively good ocular comfort on drug administration.

The FDA statistical analysis evaluated the robustness of the submitted efficacy data. The danger of using LOCF for missing data was explored, noting the potential biasing of results with this method. Sensitivity analyses using alternative population sets (PP and ITT with observed data only) and repetition of the ITT analysis with different imputation methods for missing data showed that bepotastine 1.0% and 1.5% maintained a predefined standard of clinical significance for ocular itching, satisfying this critique. In addition, the choice of p values for clinical significance evaluation was criticized for the lack of a multiplicity adjustment to account for the “majority of time points” stipulation that allows multiple ways to satisfy the clinical significance criteria. When these adjustments were made, however, the efficacy conclusions remained unchanged.

In summary, bepotastine 1.0% and 1.5% are found to be efficacious for the treatment of ocular itching related to allergic conjunctivitis, with a swift onset of action and appropriate duration of action for twice-a-day dosing. This drug does not appear to be sufficiently effective for the indication of conjunctival redness. Finally, bepotastine 1.5% solution was found to be more effective than the 1.0% concentration, so only the 1.5% concentration has been FDA approved.

Safety and tolerability

The side effect profile of bepotastine ophthalmic solution is similar to that of other ocular antihistamines, a list of uncommon or low-risk events comprising headache, asthenia, blurry vision, burning on drug instillation, cold and flu symptoms, cough, fatigue, dry eye, foreign body sensation, eyelid edema, keratitis, hyperemia, nausea, pharyngitis, pruritus, rhinitis, sinusitis, sore throat, and bitter taste. Tolerability was reported for each of the randomized trials. In addition, an unpublished safety study was undertaken to evaluate only the 1.5% bepotastine concentration at six sites in the US, and this was completed with a randomized, double-masked, placebo-controlled, parallel-group safety study design. Results of this study will be given as reported in FDA documents.

In the single-site Phase II/III trial, the number of ocular adverse events reported was greater in the placebo group (8.3% of subjects) than in either treatment arm of the study, and all events were limited to eye irritation, foreign body sensation, and a single conjunctival cyst in the bepotastine 1.5% group. Although a small number of nonocular adverse events were reported in all study groups, including placebo, only taste on instillation appears to be more common in the drug groups than in the placebo arm (20%–25% incidence in the two drug concentration groups versus 0% for placebo). Ocular and nonocular side effects were similar in the multicenter efficacy trial, revealing no new concerns, and in this instance a taste on instillation was only noted in 5% of subjects in the drug arms versus 0% in the placebo arm.

The dedicated safety study for bepotastine 1.5% tested bilateral twice-a-day dosing for 6 weeks in healthy volunteers ≥3 years old. Six sites enrolled 861 healthy subjects, randomizing to a 2:1 active:vehicle ratio. The population was predominantly Caucasian (85% of 575 subjects in the bepotastine group and 84% of 286 subjects in the vehicle group), and females outnumbered males 3:2. The pediatric population included 47 bepotastine and 25 vehicle subjects in the 3–9 year age group, as well as 40 bepotastine and 15 vehicle subjects in the 10–17 year age group. The study consisted of four visits over approximately
In summary, over a 6-week time period, twice-daily bepotastine besilate 1.5% ophthalmic solution was found to be a safe drug for subjects ≥3 years old when dosed bilaterally. No serious adverse events were observed, although abnormal taste complaints were common, found in approximately 25% of subjects across studies. Ocular comfort does not appear to be compromised by bepotastine. Although drowsiness is a common complaint due to systemic H1-antihistamines, this was not seen after ophthalmic dosing. Finally, bepotastine ophthalmic solution has not been tested in children under 3 years old or in pregnant women.

**Patient-focused perspectives**

The recent FDA approval and commercial availability of bepotastine besilate 1.5% ophthalmic solution adds to the array of treatments available for ocular itching associated with allergic conjunctivitis. Although this drug has not been directly compared with other available treatments, studies to date prove its effectiveness as well as its mild side effect profile. The twice-daily dosing strategy, although less optimal than the once-daily formulation of olopatadine 0.2% (Pataday), should lend itself to reasonable adherence and is identical to the dosing of azelastine, epinastine, ketotifen, and the 0.1% solution of olopatadine.

A key disadvantage to bepotastine is that its formulation, like most other drugs for this condition, contains benzalkonium chloride, which can be absorbed by contact lenses and is an ocular irritant to which certain patients may be allergic. It is recommended that contact lenses be removed prior to instillation of this agent. There are no preservative-free formulations of ophthalmic H1-antihistamines, so this drawback does not distinguish bepotastine.

The expense of the various ophthalmic H1-antihistamines is displayed in Table 2, with a column showing the price per day of bilateral treatment with each agent. Calculating based on retail costs, the over-the-counter ketotifen formulations are clearly the least expensive options within this class, with daily expenses of $0.26 (Alaway) or $0.56 (Zaditor). For patients who do not respond to ketotifen or who are unable to tolerate the formulations of these agents, generic azelastine bepotastine is the next least expensive ophthalmic H1-antihistamines, so this drawback does not distinguish bepotastine.

Bottle size may be another advantage of bepotastine, which is marketed as a 10 mL volume. As the days/bottle
Table 2 Retail price data for ophthalmic H1-antihistamines for relief of seasonal allergic conjunctivitis. Adapted with permission from PDR for Ophthalmic Medicines, 37th edition, 2009. Price data from Drugstore.com on 11/155/22/2010

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Product name(s)</th>
<th>OTC?</th>
<th>Doses/day</th>
<th>Bottle size (mL)</th>
<th>Price/bottle</th>
<th>Price/drop</th>
<th>Price/day (OU)</th>
<th>Days/bottle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azelastine HCl</td>
<td>Optivar</td>
<td>No</td>
<td>2</td>
<td>6</td>
<td>$115.99</td>
<td>$0.98</td>
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<td></td>
<td>Generic</td>
<td></td>
<td></td>
<td></td>
<td>$95.99</td>
<td>$0.80</td>
<td>$3.20</td>
<td>30.6</td>
</tr>
<tr>
<td>Bepotastine besilate</td>
<td>Bepreve</td>
<td>No</td>
<td>2</td>
<td>10</td>
<td>$177.31</td>
<td>$0.90</td>
<td>$3.55</td>
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<td>Emadine</td>
<td>No</td>
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<td>5</td>
<td>$78.75</td>
<td>$0.79</td>
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<td>Elestat</td>
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<td>2</td>
<td>5</td>
<td>$116.58</td>
<td>$1.17</td>
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<tr>
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<td>2</td>
<td>10</td>
<td>$12.99</td>
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<td>Olopatadine HCI 0.1%</td>
<td>Patanol</td>
<td>No</td>
<td>2</td>
<td>5</td>
<td>$116.39</td>
<td>$1.16</td>
<td>$4.66</td>
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</tr>
<tr>
<td>Olopatadine HCI 0.2%</td>
<td>Pataday</td>
<td>No</td>
<td>1</td>
<td>2.5</td>
<td>$112.20</td>
<td>$2.24</td>
<td>$4.49</td>
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</tbody>
</table>

Notes: *Largest available bottle size used for calculations; †20 drops/mL assumed. Abbreviation: OTC, over-the-counter.

column in Table 2 displays, this provides approximately 50.1 days of therapy in a single bottle, which is equal to the largest size of ketotifen and longer than any other agent. This length of time may encompass the entire season of allergic conjunctivitis for some patients who display symptoms in only part of the year. These patients would only need to purchase a single bottle of bepotastine each year, which is a distinct efficiency advantage over smaller bottle sizes.

Conclusion

A review of the available literature regarding bepotastine besilate 1.5% ophthalmic solution (Bepreve) confirms that it is a safe and effective agent for the treatment of ocular itching associated with allergic conjunctivitis. This agent does not eliminate conjunctival redness, and it should not be used in children under 3 years old or in pregnant women. Aside from these concerns, bepotastine could be widely prescribed in children under 3 years old or in pregnant women. Aside from these concerns, bepotastine could be widely prescribed and should prove to be an effective alternative to available therapies, although there are no comparative clinical data to demonstrate any difference in effectiveness between bepotastine and other ophthalmic H1-antihistamines. Although the price point for bepotastine is higher than the over-the-counter ketotifen formulations, the current retail price is lower on a per-day-of-therapy basis than the retail price of any other off-patent drugs within bepotastine’s class. Providers should feel confident in prescribing bepotastine for ocular itching associated with allergic conjunctivitis, especially for patients who have failed less expensive alternatives.

Disclosure

The authors report no conflicts of interest in this work.

References


