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Pipeline

Compared to what? The placebo effect in dry eye therapy

Several new ophthalmic drugs and biologics were approved by the U.S. Food and Drug Administration (FDA) in the past calendar year (e.g., certizine, latanoprostene bunod, and netarsudil). The ophthalmic community is pleased to see these new therapeutics for patients. However, each new approval brings the obvious question — will the experience in my patients be similar to, better than or worse than that in the controlled clinical studies? When I consider this question, I am reminded of the 1960's Jazz tune "(Trying to make it real) Compared to what?" written by Gene McDaniels.

I recall an anecdotal case of a woman in her 80's who had high myopia (- 9 D), requiring spectacle or contact lens correction since her adolescence. She had bilateral cataract extraction performed by phacoemulsification with monofocal intraocular lens implantation. The surgeries separated by a few weeks. By clinical standards, both procedures were successful, without post-operative complications or sequelae, resulting in correction-free vision. After the first procedure, the patient was ecstatic, dazzled by the quality of her vision, commenting on how yellow the bananas appeared. After the second procedure, she was unhappy, and thought her vision was worse.

A cataract surgeon advised me that many patients consider the second surgery as a failure compared with the first. Before surgery, vision is bad in both eyes, and patients believe that is the norm and everyone sees as poorly as they do. The first surgery allows more light in, enhancing color vision and acuity. The second surgery is compared to a fully recovered, good seeing first eye and patients are disappointed. Ultimately, the patients forget which eye was first or second and go on to be satisfied with their eyes. Researchers have looked at the need for second eye cataract surgery more systematically. They have found that cataract surgery in the second eye of patients with bilateral cataract is associated with clinically and statistically significant improvement in functional impairment and other measures [1–4].

During pre-approval development of a new product, the number of patients exposed to the treatment is on the order of 1500 patients.[1] For a new ophthalmic medication for a chronic indication, the minimal safety requirement in the U.S. is typically 300–500 patients exposed, at least 100 of them chronically [5]. Once approved and available, the number of patients exposed to a new product increases exponentially. The heterogeneity of the clinic population is typically much larger than in the carefully controlled pre-approval trials, with patients using more concomitant medications and having more co-morbid conditions. In some cases, a novel therapeutic may essentially be channeled into a higher risk population [6]. These differences in population could ultimately affect both the efficacy and safety of the new product.

In the 1980's, I was involved in both the pre-approval and post-approval clinical evaluation of a topical new chemical entity (NCE) in an existing class for the treatment of ocular hypertension and open-angle glaucoma. We conducted what at the time were very large and long-term studies – 400 patients at 10 sites were treated and evaluated for up to 4 years. These studies were double-masked, randomized parallel studies in which the investigational drug, levobunolol, was compared to an approved product of a the same class, timolol. Levobunolol was found to be similar to timolol in reduction of mean intraocular pressure (IOP) [7]. The product was approved first in Germany as Vistagan® and in Canada as Betagan®. We conducted post-marketing studies in both of those countries shortly after approval. In Germany, the evaluation included 2041 patients at 143 sites. In Canada, the evaluation included 425 patients at 65 sites. There were no new safety findings from the pre-approval studies– either in the nature or incidence. These were open-label uncontrolled studies, and so a comparison to a positive control such as timolol was not performed. However, one could evaluate the ocular hypotensive efficacy compared to pre-drug levels, and this was less than was seen in the controlled pre-approval studies [8,9]. In the pre-approval studies, mean reductions in intraocular pressure (IOP) ranged from 6.2 to 7.8 mm Hg from a baseline of approximately 27 mm Hg. In the post-approval studies, the mean reduction was 4.7 mm Hg in Germany and 3.2 mm Hg in Canada. We interpreted those findings as not unexpected or inconsistent with pre-approval studies, given the relatively uncontrolled nature of these studies. In the pre-approval studies, all patients were washed out of their ocular hypotensive medications, whereas there was no standardization of washout or concomitant medications in the post-approval studies. Thus, the incremental ocular hypotensive effect in the post-approval studies was expected to be less than in the pre-approval studies.

In 2018, clinical researchers are well aware of the "placebo-effect" – however, it was only ~80 years ago that Gold et al. first documented the use of a placebo and masking of patients, in order to ascertain the relative efficacy of a treatment (in this case, xanthines for the treatment of cardiac pain) [10]. The placebo effect is perhaps most notable in analgesic and irritable bowel syndrome indications [11]. However, the placebo effect is also seen in movement disorders – and the perceived efficacy may depend upon perceived cost [12]. An even more complex case occurred in the mid-2000's. Amgen was evaluating putaminal glial cell line-derived neurotrophic factor (GDNF) infusion (i.e. intracranial injections) for the treatment of Parkinson's disease. There was some question of the magnitude of efficacy, the safety of GDNF, but also whether GDNF was better than vehicle alone. Amgen stopped development, but there was legal action from patients who felt they benefited from the treatment [13–16].

[1] ICH E1: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf.

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One might think that the safety of a placebo would be obviously better than that of an active drug. However, that is not always the case. In a classic publication entitled "Adverse nondrug reactions", Reidenberg and Lowenthal surveyed 670 subjects (mostly medical students and staff). Eighty-one percent (81%) of the 414 subjects who had no illnesses and were not taking any medications stated they had experienced at least one of the list of 25 symptoms (common adverse events such as fatigue, inability to concentrate, excessive sleepiness, etc.) in previous 72 hours [17]. This study was replicated more recently, showing that there might be some relationship between personality and adverse event reporting [18].

In the treatment of dry eye, there are additional considerations. To date, the pre-approval clinical studies conducted for registration in the U.S. and Europe are vehicle-controlled, or other negative-controlled comparative trials. The vehicles used in formulating topical treatments for the eye may themselves provide both objective (signs) and subjective (symptoms) therapy. This efficacy is acknowledged in the U.S. FDA's "Over-The-Counter Ophthalmic Monograph" (21 CFR 349) [19]. More complex vehicles such as those used for molecules of relatively low aqueous solubility such as cyclosporine have efficacy as well [20,21].

In an article in this journal, Foulks reviewed the pitfalls encountered in clinical trials in dry eye disease. He discussed the peculiarities of dry eye disease with respect to symptoms, signs, and pathophysiological changes. He stated "…Potential problems that apply to all clinical trials, including patient selection, randomization in small populations, and assessment of the placebo effect, are presented with respect to dry eye clinical trials" [22]. He also presented an extensive discussion of the placebo response in dry eye trials. He noted that "… a placebo is considered a maneuver, instruction, or substance that in itself provides no benefit to the condition being treated and hence could be useful to exclude any apparent beneficial effect that would be attributable to the patient's desire to respond to therapy. A nocebo is, in contrast, a maneuver, instruction, or substance that inherently does not worsen the condition nor provoke [an adverse event], but which the patient interprets as aggravating the condition being treated or producing an unwanted adverse side effect." Foulks posits that one reason why placebo response is so profound in the treatment of dry eye disease is an improved treatment adherence by the patient. Other considerations are the ameliorative effect of discontinuing pre-study preserved agents, especially with inadequate washout. Of course, as ocular surface disease has a local nature, lubricants alone may have efficacy, in the same way that occlusive therapy may be effective in the treatment of psoriasis. One way to minimize the potential for increased treatment adherence to confound a therapeutic trial might be a run-in period on a OTC lubricant [23].

In order to gain regulatory approval in the U.S., a new drug has to provide "substantial evidence of safety and efficacy in well-controlled clinical trials" [24]. This was the case for both of the approved pharmacotherapies for dry eye disease in the U.S., Restasis® (cyclosporine ophthalmic emulsion) and Xiidra® (lifitegrast ophthalmic solution). As stated in the package insert, "…Restasis® demonstrated statistically significant increases in Schirmer wetting of 10 mm versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation. This effect was seen in approximately 15% of Restasis® ophthalmic emulsion-treated patients versus approximately 5% of vehicle-treated patients."[2] This is shown graphically in Fig. 1.[3] The Xiidra® package insert includes information on a symptom (eye dryness score) and a sign (inferior fluorescein corneal staining). Eye dryness score is shown graphically in Fig. 2 [25].

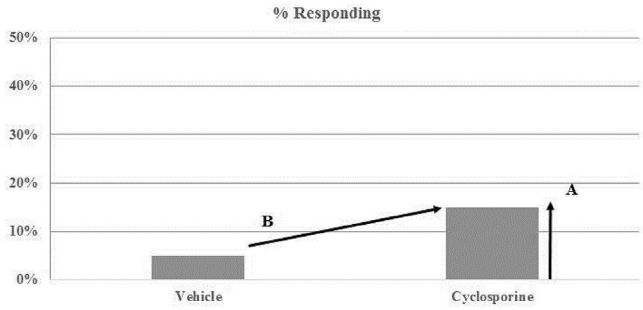

Fig. 1. Restasis® (cyclosporine ophthalmic emulsion): Proportion of patients who demonstrated increase in Schirmer wetting of 10 mm after six months of treatment. A = difference from baseline; B = difference from control. Redrawn from Restasis® U.S. Package insert.

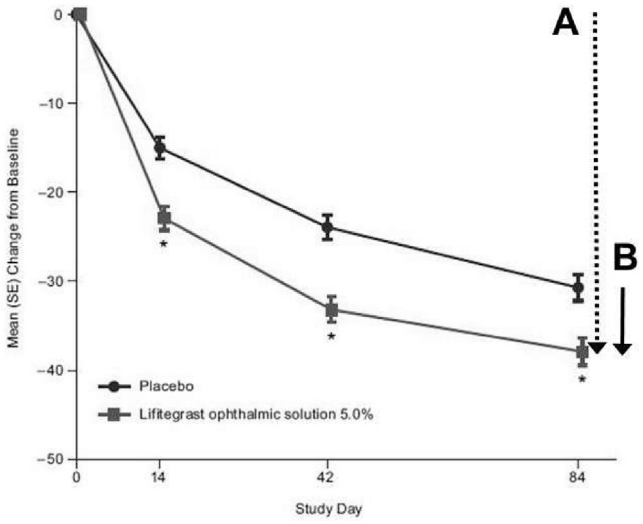

Fig. 2. Xiidra® (lifitegrast ophthalmic solution): Eye dryness score (range 0–100 points): Change from baseline. A = difference from baseline; B = difference from control. From Holland et al., 2016 [25].

Also recently granted marketing by FDA is the Allergan Neurostimulatory Device (True-Tear®). In a key study conducted for the marketing authorization, the comparison was between stimulated (electrical) and unstimulated tear production quantified by Schirmer scores.[4] This is shown graphically in Fig. 3 [26].

From a regulatory perspective, it is the difference between the active treatment and vehicle that is used in the review and approval of a new product (Line B in each figure). However, the patient typically experiences the change from baseline (Line A in each figure). By definition, Line A is bigger than Line B, as it is not adjusted for the negative control. So is this what happens in clinical practice? First, as already noted in the example for levobunolol, while the safety is similar, the efficacy is actually less in real patients. However, that is due primarily to the baseline – it is not an unmedicated baseline in "real" patients. That is an issue with patients with dry eye disease, as some are already on therapy –with OTC lubricants and possibly approved pharmacotherapies. However, this should not be a factor

[2] https://www.allergan.com/assets/pdf/restasis_pi.pdf.

[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/050790s020lbl.pdf.

[4] https://allergan-web-cdn-prod.azureedge.net/actavis/actavis/media/allergan-pdf-documents/labeling/ifu_truetear_professional.pdf.

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