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High Hurdle of Clinical Trials to Demonstrate Efficacy of Anticataractogenic Drugs

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Key Words
Controlled clinical trials · Anticataractogenic drugs · Classification system · Scheimpflug photography · Retroillumination photography · Image analysis

Abstract
Recently, the rapid progression of cataract surgical technique has led cataract patients in industrialized countries to ignore the possibilities of drug therapy. Globally, however, it will be impossible in the near future to treat cataract by surgery alone, mainly due to medicoeconomic reasons. Preventative measures must be sought. As one of the these measures, the development of anticataractogenic drugs has reemerged as a focus in the lens research field. Although clinical trials of newly developed drugs are absolutely necessary before they enter the market, they have been considered to be a rather easy task. However, in order to gain accurate and reproducible data from trials, the trial program must be carefully prepared. The numbers of participants to the trial, the selection criteria of the subjects, the objective judgment of cataractous changes, follow-up period, a high technical level for cataract documentation and image analysis are proposed. Although there still remain some difficulties concerning the methods for objective judgment, a scientifically acceptable examination must be conducted.

Introduction

Although anticataract agents are available all over the world [1], there are still no agents that have had their efficacy confirmed through reliable evaluation. On the other hand, the treatment of progressed cataract affecting vision has been almost perfectly established by the recent remarkable improvements of intraocular lens (IOL) surgery, an advancement of high importance to cataract patients and ophthalmologists in industrialized countries today. However, it is also true that the majority of people with blindness due to cataract in developing countries cannot be rescued by surgery alone, because of the situation of the economy in each country or lack of manpower in health services [1]. The numbers of IOL surgeries are continuously increasing, which has led to serious medicoeconomic problems in industrialized countries.

To find a way to overcome these problems, basic scientists in the lens and cataract research field should make a

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new effort toward the prevention of cataract development or its progression [2–8]. This is why the development of new anticataract agents has been promoted in the past as well as in the present. Until recently, despite a few clinical trials of anticataract agents that were performed in industrialized countries [2–5], many researchers seem to think that the concept of testing drug efficacy against cataract is simple. Based on the author's long-term experiences with basic and clinical studies of the lens and cataract, the high hurdle of clinical trials of anticataract agents is discussed.

The Aim of a Drug Treatment for Cataract

The aim of a drug treatment for cataract would be the prevention of risk factors which could initiate the opacification process or to inhibit the continuous progression of already existing opacities. However, since opacified lens areas are based on denaturated protein molecules, it is against all basic laws of biology and thermodynamics that it would be possible to reverse a protein denaturation in order to clarify the cataract lens again. Therefore, the aim of drug treatment makes clear that it is important to start such drug treatment as early as possible in order to save most of transparency from progression of the opacification process and thus to guarantee useful vision in case the drug has an efficacy against a fixed type of cataract. In other words, it is clear that we may be able to successfully treat one type of cataract with only one drug.

Appropriate Preclinical Animal Studies

Pharmacokinetic Study. Ocular pharmacokinetic studies in animal eyes have to be performed and should be made available to clinical investigators before beginning clinical trials. Later human studies have to supplement the animal data.

Targeted Type. Furthermore, the investigators should be informed which type of cataract will be targeted by the agent. However, they are usually not clearly informed about these two fundamental matters. For illustration, a pharmacodynamic study on aldose reductase inhibitor (ARI, AD-5467, Senju, Japan) in rat eyes [6] and an efficacy study on a vitamin E (V-E) ophthalmic solution against steroid-induced subcapsular cataract in rat eyes [7] will be described. The concentration and administered dose of applied ARI and V-E solution were 0.4% (5 μl × 4 daily) and 5% (10 μl × 2 daily), respectively. The efficacy of the agents was objectively evaluated through photographed Scheimpflug images of the lens (fig. 1a, b) [6]. The intraocular penetration of ARI eye drops in normal rat eyes and that in streptozotocine-induced cortical lens opacification is shown in figure 1c [6]. The rat eye study proved drug efficacy against induced diabetic lens cortical opacification in rat eyes. Although the level of aldose reductase in human lenses is not as high as it is in rat lenses, the information from the rat study would at least be helpful to investigators who plan to perform clinical trials. In order to prove the efficacy of V-E eye drops for (sub)cortical cataract, the authors' data from a rat steroid-induced cataract model [7–9] are shown. Typical subcapsular opacification was remarkably suppressed by the treatment of V-E instillation. Although the efficacy of either locally applied or systemically administered V-E to deep-layer cortical and nuclear cataract has not been proven experimentally, clinical studies on V-E trials (oral) are now being conducted [4]. Proof of the efficacy in animal models is expected.

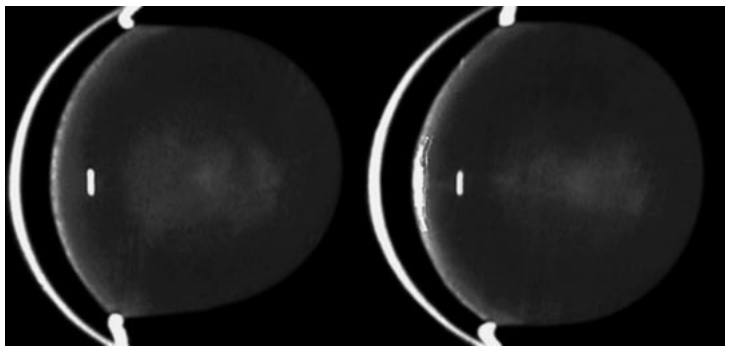
Indication for Drug Application

Lens Transparency Changes with Ageing. According to population-based epidemiological surveys in Japan, around 45–60% of people in their 50s had transparent lenses, and for people in their 60s and 70s this figure drops to 35–20% and 15–5%, respectively. The prevalence of clinically apparent cataract according to the classification system of the Japanese Cooperative Cataract Study Group [10, 11] in subjects in their 50s and 60s was around 15 and 25–30%. Since no gender difference was seen in the two groups, the preferable age-groups of trial cases would be the 50s to 60s [12, 13].

Prevalence of Cortical, Nuclear, Subcapsular and Mixed Type Cataracts by Age and Gender. The prevalence of pure types of cortical opacification decreases with ageing (fig. 2). The important matter is that the targeted type should be clearly indicated in the clinical trial inclusion criteria. Subjects over 70 would not be preferable participants of the trial, because of their higher age and mixed type of cataract.

Difficulty in Gathering Subjects

Agreement to Participate in a Clinical Trial with Use of a Placebo. In any trial, informed consent is absolutely required today. However because of long-term observation, investigators sometimes encounter an ethical prob-



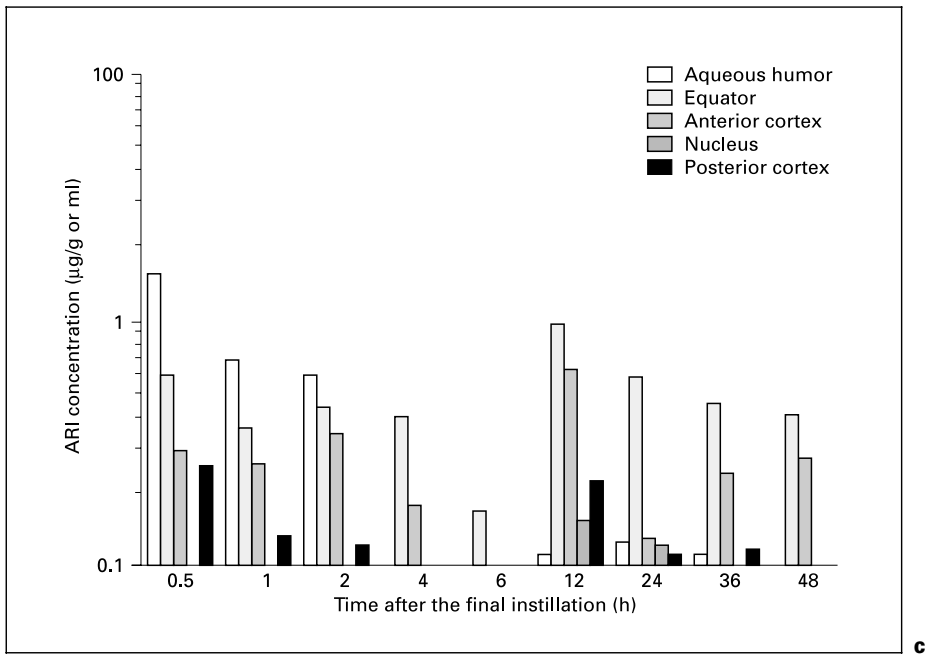


Fig. 1. a, **b** Representative lens condition 9 days after the start of ARI treatment: DM + ARI group (**a**), DM control group (**b**). **c** Time course of AD-5467 penetration into the eye.

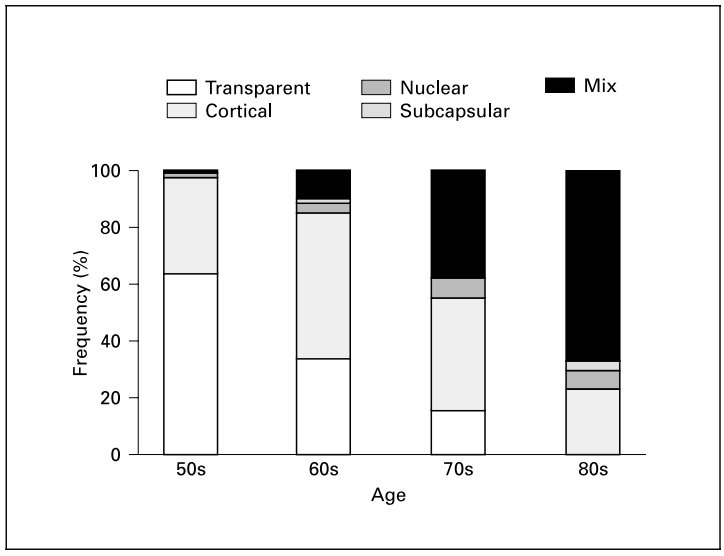


Fig. 2. Cataract prevalence by type and age (Monzen study in Japan) [13].

lem when the study design uses a placebo group. At least in Japan, it is quite difficult to gather enough participants when they are clearly informed about the background of the study. The same tendency may occur in other countries. The number of patients depends on the sensitivity of the Scheimpflug or the retroillumination method and their error probability. Another question is how long do we have to monitor the treated and the untreated eyes for a significant difference. This can be calculated by statisticians [14].

To Confirm Good Compliance. Investigators should strictly check the participants' drug compliance [15]. Without periodical visits of the participants to the investigator, the final data may include some inappropriate usage. The kind of periodical visit to the investigator can be difficult for the participants, in particular in their late 50s and early 60s, who are still actively involved in their daily activities.

Dropout Ratio. According to the authors' experience in a clinical trial, 18% (9 out of 50) of the participants dropped out by the 6th month and 30% (15 out of 50) by the 12th month. If a 2-year observation period is needed, the ratio may even exceed 30%.

Number of Participants and Multicenter Studies. Of course it is ideal to have a large number of participants, but in order to realize this, a multicenter study is unavoidable. However, since photographed images of the lenses for the evaluation of drug efficacy will be applied, the technical level of the investigators must be high and each investigator and camera operator should understand the difficulty of the examination. Although this may appear to be easy to investigators, the authors would like to emphasize what an unbelievably hard task it is. Since detectable significant changes of the lens are usually small, the results will be incorrect if the data are not highly reliable.

Judgment

Cataract Grading with the Help of Standard Photos. The cataract grading system to be applied in the trial should be discussed before the trial begins. Although several systems with several steps have been proposed, only the LOCS III [16] system, with the help of standard photos, has six grading steps. However, lens changes that occur during the observation period are small and may be classified in the same range. In particular, precise changes in the nuclear area cannot be detected through slitlamp microscope observation alone. If the investigators aim to test an applied anticataract agent on a rather progressed cataract, a rough judgment of increasing opacification will be possible. At least at present, no agents have a miracle cure mechanism to diminish lens opacification. Because of this, investigators should seek better and more objective methodologies.

Limitation of Photographic Approach. In order to make judgment as objective as possible, Scheimpflug photography through cameras such as the Topcon SL-45 [17], SL-5E [18], Nidek EAS-1000 [19], Zeiss SLC-System [20] and CASE-2000 [21] and retroillumination photography by Neitz CT-R, SL-5E (Topcon), EAS-1000 (Nidek) and CASE-2000 cameras have generally been applied. Regarding the slit findings of cataractous lenses, Scheimpflug images are the most suitable for detecting nuclear changes [22], however, Scheimpflug photography is not quite as good in the judgment of cortical cataract, which may be the type of opacification targeted most frequently in the clinical trials. A three-dimensional type of image analysis which can overcome the above disadvantage has been established [23], but it is still only at the research level and seems to be very complicated for a long-term controlled clinical trial with a large number of patients. On the other hand, retroillumination imaging seems to be suitable for recording the state of cortical opacification, but when the opacification in multilayers overlaps, accurate judgment becomes difficult. Although the EAS-1000 can take retroillumination images at different focussing planes, this system is still unsatisfactory to the authors who developed it. Notwithstanding, the authors have applied retroillumination photography to trials of anticataract agents. If the subjects in the trial are chosen with limited criteria, such as a quite early cortical cataract, the cataractous shadow between the anterior and posterior cortical layers will not overlap. Images taken through a dilated pupil, which reduces several kinds of noise (fig. 3) that may lead to incorrect judgment, would be worth applying to the clinical studies.

Reproducibility of the Photographed Images in Multicenter Studies. Reproducibility of photography will directly relate to the success of the trial. It is essential that the cameras applied in the trial should be standardized [24–26]. Furthermore, investigators involved in the trial should have almost the same level of photographical technique, and data analyzers must use the same scale of judgment, if the data is judged separately. For example, the cortical cataract shadow size area in a retroillumination image is influenced by the pupil diameter, even when these images have no troublesome noise (fig. 4). To compare the results by different analyzers, 5 researchers who

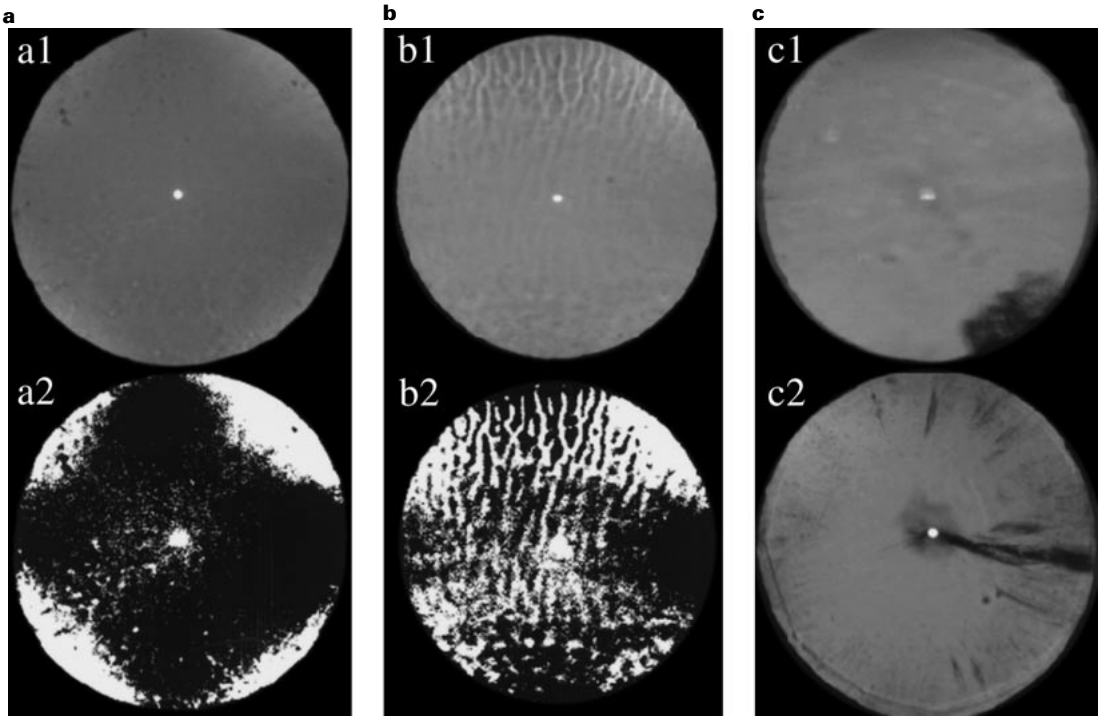


Fig. 3. Noise noticed in the retroillumination images. **a** Dark cross due to the polarization property of the cornea (a1 = original, a2 = binary image processed by threshold method). **b** Turbulence of precorneal tear film (b1 = original, b2 = binary). **c** Out of focus (c1 = eye movement, c2 = a case of overlapping anterior cortical opacity and posterior subcapsular opacity).

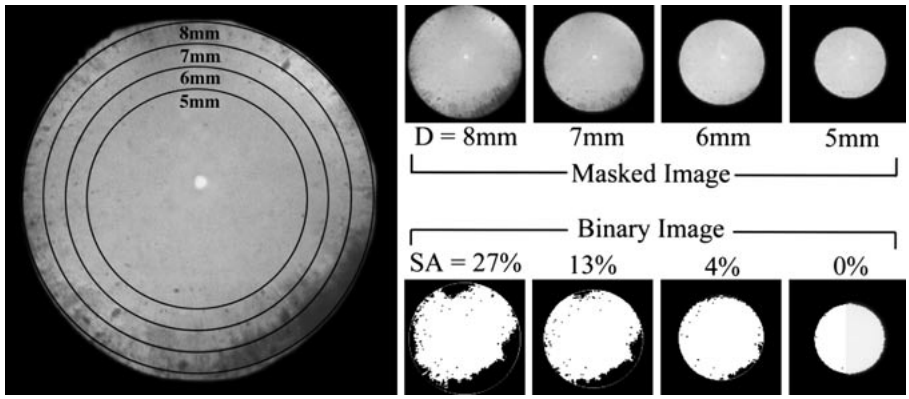


Fig. 4. Pupil sizes and shadow areas.

were familiar with lens photography were selected and asked to take a training session before the testing on cataractous shadow measurement through retroillumination images. The test samples were 9 eyes with three different image qualities (A = appropriate pupil size, B = too large pupil size, C = irregular pupil size). Each analyzer was asked to calculate the shadow area separately, three times. Figure 5 shows the reproducibility of their measurement. Even when noise such as corneal tear film, dark cross due to the polarization property of the cornea, Purkinje-Sanson' images and focussing seen in the retroillumination images is reduced, the preferable error range is ± 5%. Since a new approach to avoid the above noise is developed by the authors' study group [unpublished method

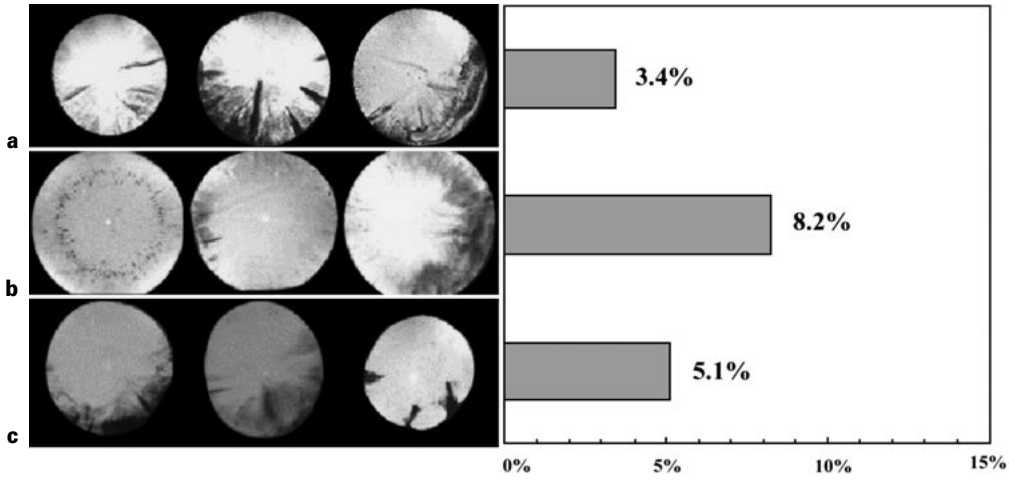


Fig. 5. Measurement error of the cataractous shadow area from retroillumination images. Five examiners who received a training session before starting the examination took nine retroillumination images three times and measurement of shadow areas was performed by each of them. **a** Good quality with appropriate pupil size; **b** with large pupil size; **c** with irregular pupil shape.

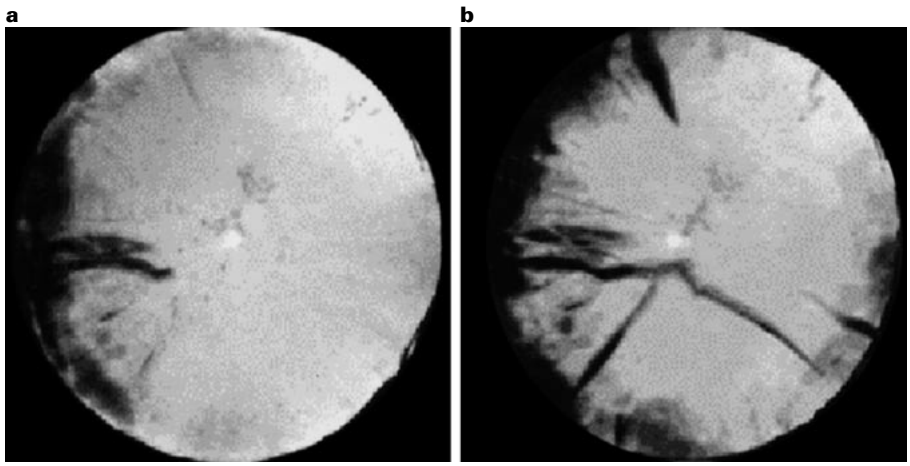


Fig. 6. Case of 59-year-old female. **a** Before starting observation (shadows are 14.9% of the 7-mm pupil size). **b** 4 years later (32.3% of the 7-mm pupil size).

presented at the Scheimpflug Club Meeting 1999, Stockholm], the quality of cortical cataract judgment will become more reliable in the future.

Follow-Up Period and Duration of Studies Using Scheimpflug Slit and Retroillumination Images

Figure 6 shows a case of progressing cortical cataract detected through retroillumination images. This case has grade I opacification by the applied system and prominent progress was detected 4 years after the initial examination. Ideally the duration of this kind of study would be 2–3 years, but a trial period over 2 years is too long for the participants today. Furthermore, a long-term trial would not be appropriate for keeping good and constant compliance. In order to overcome the above hurdles, data analysis methods which are able to detect small changes with high reliability have to be developed. The equatorial area of lenses at an early stage of cortical cataract sometimes shows increased light scattering intensity in an area that looks transparent during a long-term follow-up period. Figure 7 shows light scattering intensity changes seen in the anterior cortex for 12–18 months after administration of V-E eye drops or control ophthalmic solution. If the increase in intensity is significantly over its normal range for age (fig. 8), information from Scheimpflug photography would be worth using to evaluate cortical cataract progression. Although there have been no investigations that confirm the above concept, a study of this type of analysis should be done as early as possible.

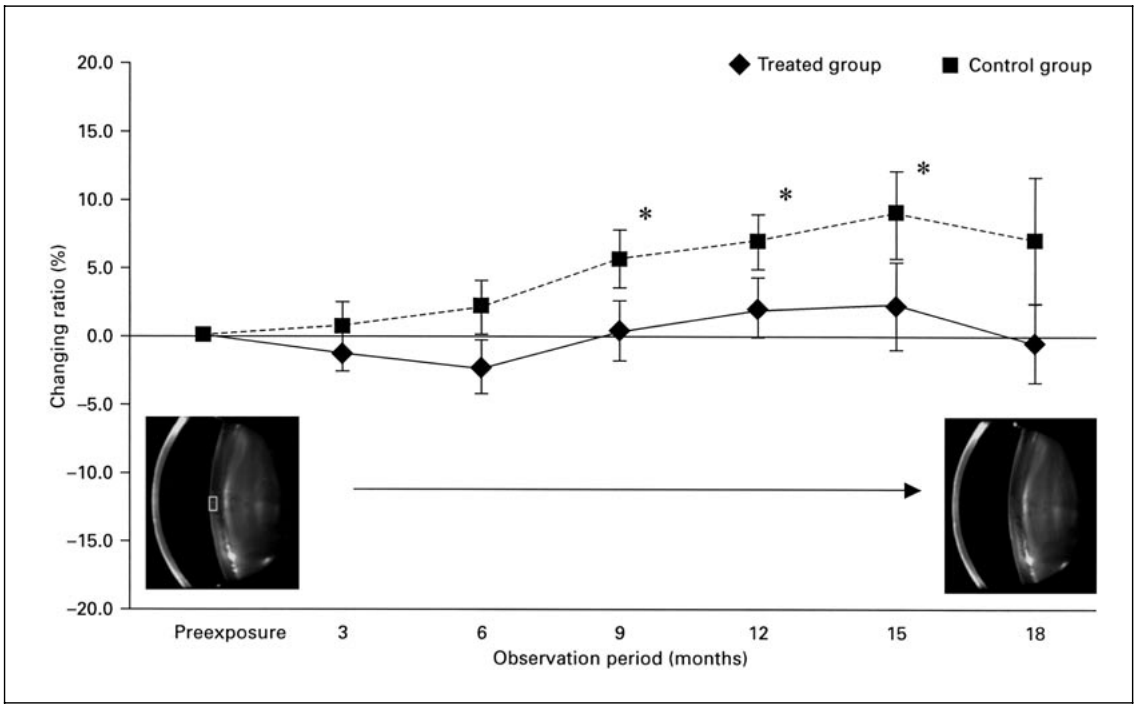


Fig. 7. Light scattering intensity changes seen in the anterior cortex 12–18 months after administration of V-E eye drops or control ophthalmic solution.

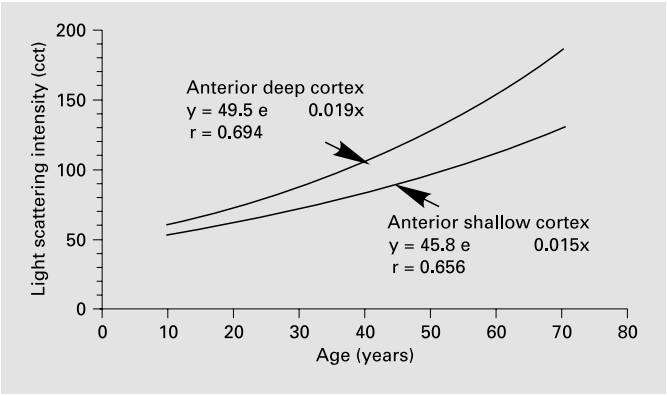


Fig. 8. Correlation between age and light scattering intensity in subjects with normal lenses.

Statistical Methods

The focus of analysis is usually on the group mean values as shown in the example of figure 7, but lens transparency changes and cataractous changes in individuals are much more important than those shown by mean values of groups [14]. Figure 9a shows changes of opacification shadow areas in the same subjects as those in figure 7, and figure 9a shows the results obtained from the group mean value. Although significant differences of shadow areas between the initial and the final data were seen, according to the analysis of figure 9b, all of the treated eyes were in the same range for 18 months. For ideal analysis, age-matched subjects are preferable. Furthermore, observers have to recognize that the analyzed data at the start of trials are quite important, since a decrease in lens transparency and progress of cataract even at an early stage directly influence the final data.

Recommendations for Controlled Clinical Trials to Test the Efficacy of Current Anticataract Drugs

At present, at least the European Lens Research Groups [14, 15, 24, 25, 27, 28] understand the importance of conducting clinical trials to test the efficacy of anticataract agents according to the guidelines recommended by the WHO Regional Office for Europe [29].

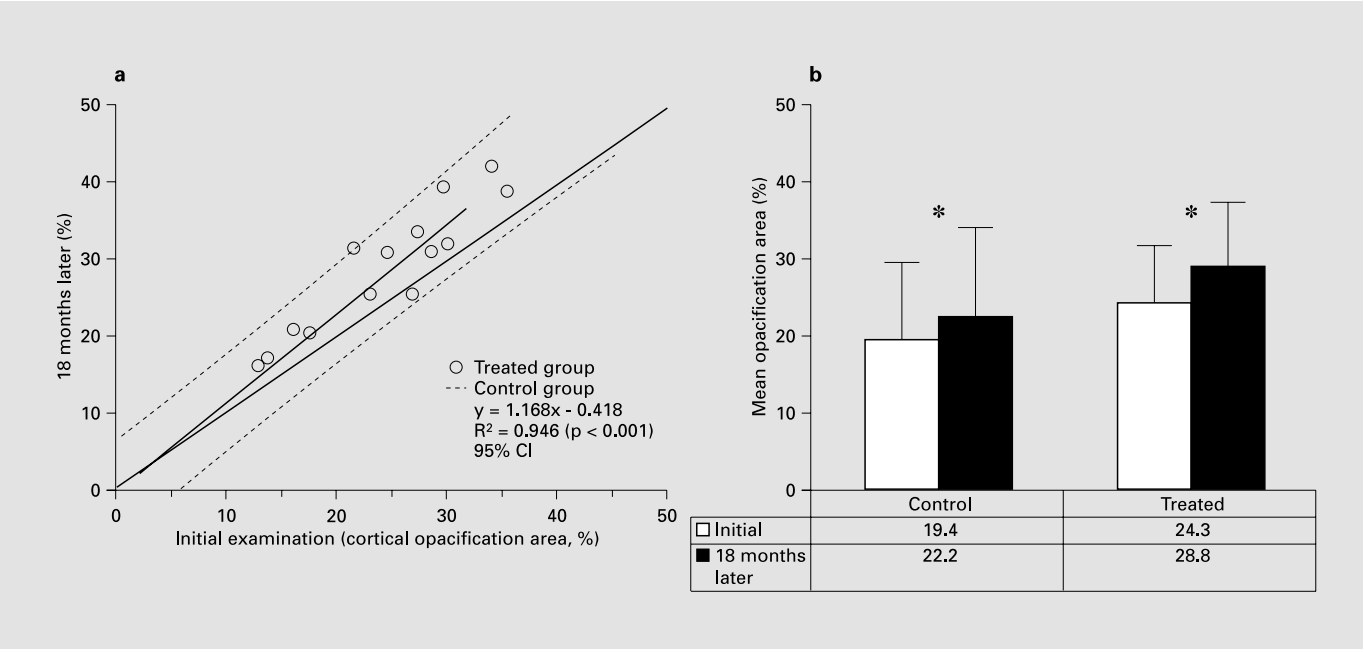


Fig. 9. Changes of cortical opacification shadow area in retroillumination images. Cortical group: mean age = 65.9 ± 9.7 years, n = 16 eyes; treated group: mean age = 72.6 ± 7.6 years, n = 14 eyes; significant difference: * $p < 0.01$.

The recommendations consist of: (i) the classification of cataracts according to the type of lens opacification; (ii) the use of preparations and placebo; (iii) a double-masked study with randomization of patients where the preparations tested are entered under a code, the key being unknown to all investigators involved; (iv) homogeneous composition of the two treatment branches with respect to cataract type and age; (v) baseline examinations with follow-up examinations conducted about 6–12 months apart; (vi) the duration of the study should be at least 2 years, but preferably 3–5 years; (vii) outline of the inclusion criteria; (viii) outline of exclusion criteria (other eye disease, diabetes, etc.); (ix) interim evaluation after 1 year so that in the case of efficacy the placebo population does not remain untreated for an unnecessarily long period; (x) the documentation of side effects; (xi) the control of patient's cooperation/compliance, and (xii) documentation of dropouts.

Although most of the above items are still valid today, some items such as documentation, classification systems or the duration of the follow-up time have been altered due to the progression of applied methodologies during the past 15 years. Among the above matters, the judgment of cataractous changes by objective, reliable and highly reproducible methods is very important. Slitlamp biomicroscopic observation alone is no longer worth applying even with other kinds of clinical examination data such as deterioration of visual acuity or abnormal glare and/or contrast sensitivities. These data are only for reference.

Presently recommendable for the judgment of lens opacification are lens images taken by special cameras for cataract research [17–21, 24–28, 30]. From the two different types of images taken by Scheimpflug and retroillumination photography, Scheimpflug slit images show more detailed and reliable data, in particular for the judgment of early changes in the nucleus and when the new grading system described in a previous report is applied [22]. Incipient pathological lens transparency can only be detected layer by layer from Scheimpflug slit images. Even though three-dimensional Scheimpflug images also offer a most suitable method to monitor cataractous changes, this technique is not yet widely used at present. However, when the cortical cataract is the main target of a clinical trial, the researchers have to determine the opacification figure at the whole lens level, even with the technological limitations of retroillumination lens photography. At present, the preferable methodology utilizes the new image analysis techniques which aim at eliminating the noise found in retroillumination photography as previously described.

Although we still do not have a perfect methodology for the judgment of all types of cataract, researchers may feel the urge to be involved in this kind of clinical study. According to the authors' experience, small cataractous changes can be detected during a period that may be shorter than the 2 years' trial period recommended in (vi). The trial period should be long enough but in order to avoid the collection of useless data, researchers should pay attention to basic but important matters discussed in this article.

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