(Appendix 1)

Guidance on evaluation of allogeneic iPS-like cells derived retinal pigment epithelial cells

1. Introduction

Basic technical requirements for ensuring quality and safety of products obtained by processing human-derived allogeneic induced pluripotent stem cells (iPS cells) or induced pluripotent stem-like cells (iPS-like cells) (hereinafter referred to as "Human (allogeneic) iPS (-like) cell processed products") are defined in the "Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (Allogeneic iPS (-like) cells)" (PFSB Notification No. 0907-5, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare [MHLW]).

The guidance on evaluation provides, in addition to the above basic technical requirements, considerations specific to a particular class of human (allogeneic) iPS (-like) cell processed products that are used as regenerative medical products applied for treatment of retinal pigment epithelial disorders, etc. The term "Regenerative medical products" is defined in Article 2, Paragraph 9 of the Pharmaceutical Affairs Law amended pursuant to provisions in Article 1 of the Act No. 84 of 2013 (Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices).

2. Scope of the guidance on evaluation

The guidance on evaluation provides, in addition to the basic technical requirements, points to consider for evaluation of quality, efficacy, and safety of a particular class of human (allogeneic) iPS (-like) cell processed products that are used as regenerative medical products applied for treatment of retinal pigment epithelial disorders, etc.

3. Positioning of the guidance on evaluation

The guidance on evaluation, which applies to human (allogeneic) iPS (-like) cell processed products currently undergoing remarkable development of technologies, provides only points to consider at the present time, but does not intend to cover considerations comprehensively. It is supposed to be revised in response to further technological innovation and accumulation of knowledge and thus not binding on application data.

Product evaluation requires scientifically rational flexibility with full understanding of characteristics of individual products.

In addition to the guidance on evaluation, other related guidelines in and outside Japan should be referred to.

4. Definitions of terms

Terms used in the guidance on evaluation are as defined in the "Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (Allogeneic iPS (-like) cells)" (PFSB Notification No. 0907-5, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW) or defined as follows.

(1) Retinal pigment epithelial cells: The term refers to cells forming the outermost layer of the 10-layer retina. They are epithelial cells forming a monolayer, phagocytose photoreceptor cells, produce visual pigments such as retinal, and constitute the blood retinal barrier. A primary lesion of age-related macular degeneration occurs involving the cells.

(2) Photoreceptor cells: The term refers to one type of cells constituting the retina. Photoreceptor cells can be simply called photoreceptors and convert light energy into electrical energy. Located in the outermost layer of the neuroretina, the tip part called the outer segment is constantly phagocytosed by the retinal pigment epithelial cells, being replaced with a new outer segment.

(3) Source materials: The term refers to original materials of raw materials or materials used in manufacture of drugs, etc. (as defined in the Standards for Biological Raw Materials [Public Notice of the Ministry of Health, Labour and Welfare No. 210 of 2003])

(4) Cell bank: The term refers to a collection of a substantial number of aliquots with uniform composition filled in containers stored under a certain storage condition. That is, each container contains an aliquot of a single pool of cells. (as defined in the ICH Q5D "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" [PMSB/ELD Notification No. 873, dated July 14, 2000, of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare or MHW])

(5) Cross-contamination: The term refers to unintentional transfer of substance from one sample to another sample. It is also referred to as contamination between samples. It means contamination between raw materials used for manufacturing and between intermediates. Potential cases are, for example, where cells derived from a cell bank are unintentionally transferred into a cell population from another cell bank; and where a pre-virus-inactivation raw material is unintentionally transferred into a batch of the post-virus-inactivation raw material.

(6) Phagocytotic capacity: Retinal pigment epithelial cells, like macrophages, are capable of ingesting foreign substances (e.g., bacteria, cellular debris) into their own cells and digesting them. In a normal state, they intake the tip part of photoreceptor cells constantly.

(7) Cell sheet: The term refers to a sheet formed by cells, which are bound to each other.

(8) Barrier function: Retinal pigment epithelial cells are bound via an adhesive structure to each other, not allowing substances to move freely. This function is called barrier function.

(9) Subretinal transplantation: The term refers to a surgical treatment in which tissues, instruments, etc. are inserted in a space intentionally made in the subretinal cavity (between the sensory retina and retinal pigment epithelial cells).

(10) Ophthalmoscopy: The term refers to an examination in which the fundus is exposed to light inserted from the front of the eyeball through the pupil and observed for changes in the retina and choroid using an indirect ophthalmoscope, retinoscope, direct ophthalmoscope, etc.

(11) Fluorescein angiography: The term refers to observation and photography examination of the fundus after intravenous administration of a fluorescent substance (e.g., fluorescein) using a specialized camera. The examination allows assessment of hemodynamics in the fundus and barrier function as well as detection of neovessels.

(12) Optical coherence tomography: The term refers to examination allowing observation of living retina's cross-sections and is abbreviated to OCT This modality excels in detecting choroidal neovascularization, retinal detachment, etc.

(13) Exudative lesion: The term refers to a pathological site of choroidal neovascularization associated with age-related macular degeneration. Subretinally accumulating exudate or

neovascular tissue in this lesion disturbs the retinal structure, causing a rapid and severe decrease in visual acuity.

(14) Dry type: The term refers to one type of age-related macular degeneration. It mainly manifests as atrophy of retinal pigment epithelium, photoreceptors, and choriocapillaris. It does not cause a rapid decrease in visual acuity but finally results in loss of reading acuity. In Europe and the United States, 80% of age-related macular degeneration cases are classified as dry-type.

(15) Electrophysiological examination: The term refers to examination that detects a weak shift of electrical potential of the retina, optic nerve, etc. made in response to photic stimulation. The examination includes electroretinography that records action potential of the retina, visual evoked potential examination that measures brain waves produced by the optic nerves or brain, and electrooculography that measures a shift of electrical potential produced by eye movement, etc. They assess functions of the retina, optic nerves, and visual center and check for abnormal eye movement.

(16) Central visual acuity: The term refers to one of the visual functions that are commonly measured in visual acuity tests. The 2-point discrimination ability (resolution) at the center (corresponding to the macula) of the visual field, which provides vision of the highest resolution, is assessed. Whether character or graphic shapes can be perceived (the Landolt rings [with a gap like the letter C] are often used in Japan) is determined.

(17) Retinal sensitivity test: The term refers to a test that examines the visual field of a subject by projecting small lights of varying brightness on different points of the retina. The test can be performed by microperimetry or static perimetry.

(18) VFQ-25: The term refers to the Visual Function Questionnaire 25 developed by the National Eye Institute in the US. The Japanese version is available. It can quantify vision-related QOL. It is used to assess effects of eye diseases on daily life and outcome of treatment and care.

(19) Fundus autofluorescence: The term refers to fluorescence emitted by lipofuscin accumulated mainly in the retinal pigment epithelium. Fluorescence density is measured using a fundus camera equipped with a dedicated filter, and the obtained data can be used to assess the function of retinal pigment epithelium.

5. Points to consider for evaluation

For the time being, the guidance on evaluation is intended to apply to evaluation of retinal pigment epithelial cells as human (allogeneic) iPS (-like) cell processed products. The cells to be evaluated are manufactured at the manufacturing site where human (allogeneic) iPS (-like) cells (cell line) established as a cell line and already used as a source material of regenerative medical products are accepted and processed. To establish human (allogeneic) iPS (-like) cells from somatic cells and manufacture regenerative medical products using the established cells as a source material within the same manufacturing site, not only the guidance on evaluation but also the “Guidelines on Ensuring Quality and Safety of Products Derived from Processed Cell and Tissue (Allogeneic iPS (-like) cells)” (PFSB Notification No. 0907-5, dated September 7, 2012, of the Pharmaceutical and Food Safety Bureau, MHLW) should be referred to.

(1) Raw materials

[1] Human (allogeneic) iPS (-like) cells used as a raw material

Used as a raw material, cell banked human (allogeneic) iPS (-like) cells should be from a cell line of human (allogeneic) iPS (-like) cells established as a source material for regenerative medical products, which needs to be confirmed or reasonably expected to differentiate into retinal pigment epithelial cells through a certain manufacturing process. If

possible, genome sequencing should be performed to rule out mutations in genes related to functions of retinal pigment epithelial cells. Genes potentially affecting functions of retinal pigment epithelial cells include ones encoding RPE65, bestrophin, SEMA4A, LRAT, RDH12, RP9, and RP11.

For human iPS cells established through genetic reprogramming by transfection with reprogramming genes in human somatic cells, presence of residual transgenes should be ruled out if possible. If the presence could not be ruled out, the transgenes should be demonstrated to have no adverse effects on quality or safety of the final product, retinal pigment epithelial cells.

If possible, infection with viruses commonly found in retinal pigment epithelial cells (e.g., human herpes virus) should be ruled out by tests performed in accordance with ICH Q5A ("Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" [PMSB/ELD Notification No. 329, dated February 22, 2000, of the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHW]). Viruses potentially infecting retinal pigment epithelial cells are mainly human herpes virus (HHV). Of 8 types of HHV (1-8), HSV-1 (HHV1) (Reference 1), HSV-2 (HHV2) (Reference data 2), VZV (HHV3) (Reference data 3), EBV (HHV4) (Reference data 4), CMV (HHV5) (Reference data 5), HHV6 (Reference data 6), etc. are known to cause infections.

[2] Donor eligibility

Because the transplantation site of the final product is close to the brain, medical conditions concerning transmissible spongiform encephalopathy, suspected transmissible spongiform encephalopathy, and other dementia should be inspected through medical history taking and interview. Based on the obtained information and presence or absence of prior blood transfusion and transplantation therapy, whether the individual is eligible for donation should be determined. If possible, the risk of hereditary retinal degenerative diseases should be checked by interview, etc.

(2) Matters warranting special attention in the manufacturing process

For manufacture of retinal pigment epithelial cells (final product), the manufacturing method should be clarified and validated for the following items to the extent possible to ensure certain quality.

[1] Presence or absence of lot configuration and specification of lot

Whether the final product and intermediate product are manufactured on a batch basis or not should be clearly stated. If it is manufactured on a batch basis, definition of a batch should be provided.

[2] Manufacturing method

The manufacturing method up to release of the final product should be outlined, including acceptance of human (allogeneic) iPS (-like) cell lines to be used as a source material at the manufacturing site and generation of human iPS cells used as a raw material and adequately differentiated cells. In addition, the treatment, necessary process control, and quality control should be specified in detail.

a) Acceptance inspection

For the human (allogeneic) iPS (-like) cell lines to be used as a source material, test and inspection items for acceptance at the manufacturing site (e.g., visual inspection, microscopic examination, viability, characterization of cells, and tests to deny bacteria, fungi, viruses, etc. contamination) should be specified with the criteria for each item. Where necessary and possible, tests for bacteria, fungi, viruses, etc. should be performed to the extent that would not affect the phenotype, genetic traits, characteristics such as specific functions, cell viability, or quality. If the result is positive, stock of the human

(allogeneic) iPS (-like) cell line and the transportation should be checked for contamination, and a human (allogeneic) iPS (-like) cell line should be obtained again.

If testing with a very partially processed material is appropriate because of technical reasons, the tests should be performed at an appropriate timepoint after acceptance. At a stage prior to the start of a clinical trial, values measured with test samples obtained to date should be presented, and based on them, provisional values should be indicated.

b) Preparation of cells to be used as a component of the final product

A method of preparing the cells, to be used as a component of the final product, from the human (allogeneic) iPS (-like) cell line accepted at the manufacturing site (including a differentiation induction method, methods of isolation and culture of intended cells, medium at each stage of culture, culture conditions, culture period, and yield) should be specified and justified to the extent possible.

c) Cell banking

If cells are banked at any stage in manufacture of retinal pigment epithelial cells (final product), for example, they are generated from the human (allogeneic) iPS (-like) cell line accepted at the manufacturing site, the reason and methods for generation, characterization, storage, maintenance, control, and renewal of cell banks as well as procedures related to other operation processes and tests should be clearly described in detail with justification. ICH Q5D, etc. should be referred to. However, a part of investigation matters may be omitted if justified by evaluation completed in the upstream process.

d) Measures to prevent mix-up and cross contamination during the manufacturing process

In the manufacture of retinal pigment epithelial cells derived from human (allogeneic) iPS (-like) cells (final product), prevention of mix-up and cross contamination during the manufacturing process is of importance, and the preventive measures in the process control should be specified.

(3) Quality control of products

If quality specification values are established at a stage prior to the start of a clinical trial, values measured with test samples obtained to date should be presented, and based on them, provisional values should be indicated. If technical difficulties preclude tests with the released product itself or a part of it, specification tests with products manufactured in parallel should be performed after being justified.

[1] Characterization Items for establishment of quality specifications for retinal pigment epithelial cells

a) Shape

Cell morphology specific to retinal pigment epithelial cells (e.g., brown pigment, polygonal and cobblestone-like cell form) should be confirmed under a phase contrast microscope, etc.

b) Characteristics specific to retinal pigment epithelial cells

Expression of a gene related to retinal pigment epithelium (any of RPE65, CRALBP, MERTK, BEST1, etc.) should be confirmed.

c) Purity

Purity of the product should be determined based on characteristic morphology or by immunostaining using multiple antibodies against RPE65, bestrophin, PAX6, etc. Or it should be determined based on expression of genes related to retinal pigment epithelium which is required to be at a certain level. Of cells with the characteristic morphology, ones containing pigment are mostly deemed as retinal pigment epithelial cells. Purity may be determined from the count of cells containing pigment objectively quantified by image processing, etc.

d) Absence of undifferentiated cells

According to literature, presence of undifferentiated cells may be assessed by flow cytometry in combination with immunostaining of undifferentiated cell markers (OCT3/4, Sox2, TRA-1-60) or by quantification of marker genes by quantitative PCR (assessment based on expression levels of genes such as OCT3/4, NANOG, and LIN28, determined by a one-step 45-cycle quantification regimen, etc.) Of the marker genes, LIN28 gene is highly specific to undifferentiated cells and provided with a highly sensitive quantitative analysis, which can be commonly used as a representative assessment method (Reference data 7).

It should be noted that presence of undifferentiated iPS (-like) cells does not necessarily lead to tumorigenicity. For tumorigenicity studies, the nonclinical study section should be referred to.

e) Functions

To confirm that the produced cells have functional properties of retinal pigment epithelial cells consistent with the intended treatment use, the in-process product should be analyzed. The following functions may be tested.

- Phagocytotic capacity (intracellular uptake of fluorescence-labeled photoreceptor outer segments, fluorescent beads, etc., which were added to a culture medium, is assessed by flow cytometry, etc.)
- Secretion capacity of growth factors (amounts of vascular endothelial growth factor [VEGF], pigment epithelium-derived factor [PEDF], etc. secreted are determined by enzyme-linked immunosorbent assay [ELISA]).

[2] Characterization Items for establishment of quality specifications for retinal pigment epithelial cell sheet

Before characterization of a retinal pigment epithelial cell sheet, the shape, mechanical suitability, and functional properties should be evaluated as described below, and the manufacturing process of the sheet should be justified as well.

a) For shape, for example, preparation of tissue sections of the sheet and 3-dimensional observation under a confocal microscope should be performed to confirm that the cells form a sheet.

b) For mechanical suitability, after operations ranging from removal of the cell sheet to preparation of a graft, whether the graft is intact as the sheet should be checked.

c) To evaluate functional properties (barrier function), an analysis on expression of appropriate markers reported to correlate with barrier function, which are identified by immunostaining (using antibody against ZO-1), etc. or trans epithelial electrical resistance (TEER) measurement should be performed.

(4) Nonclinical studies

[1] Quality control of the final product or tumorigenicity studies for nonclinical safety evaluation

When tumorigenicity of regenerative medical products manufactured by processing human (allogeneic) iPS (-like) cells is evaluated, it should be noted that "correlation and causal relationship between tumorigenicity of iPS cells used as a raw material and that of the final product remain to be elucidated." That is, it must always be noted that for clinical application, in tumorigenicity evaluation, the greatest importance is attached to the final product, a human (allogeneic) iPS (-like) cell processed product but not human (allogeneic) iPS cells used as a raw material. Tumorigenicity studies should be conducted with the final product. Tumorigenicity evaluation using a study system in immunodeficient animals with the known detection limit is useful.

There are two major types of tumorigenicity evaluation of the final product according to the purpose. Tumorigenicity studies are conducted for the purpose of "quality control" (to check an amount of tumorigenic cells present in the final product) or for the other purpose of "nonclinical safety evaluation" (to check whether cells in the final product exhibit tumorigenicity in a microenvironment corresponding to the administration site in humans). Tumorigenicity evaluation must be performed with either of the two purposes specified. For the former purpose, for example, subcutaneous dose studies in immunodeficient animals (e.g., NOD/SCID/γC^{null} (NOG) mice [Reference data 8, 9], NOD/SCID/IL2rγKO (NSG) mice, Rag2-γC double-knockout (DKO) mice), which allow simple observation and are highly sensitive, may be conducted. For the latter purpose, for example, subretinal dose studies in immunodeficient animals may be conducted (Reference data 9, 10, 11). Quality evaluation for tumorigenicity of the final product can be performed by methods other than subcutaneous dose studies in immunodeficient animals. A useful method may be *in vitro* determination of an amount of residual undifferentiated cells in the final product. The *in vitro* determination may be performed by flow cytometry (e.g., TRA-1-60) or quantitative RT-PCR (e.g., *LIN28*) using undifferentiated cell marker molecules as indicators (Reference data 7). Regardless of the method adopted, the detection limit of the study system must be identified before interpretation of the results.

Because subretinal (clinical route of administration) transplantation involves a surgical procedure, which is highly invasive especially in small animals, it should be noted that the surgical procedure could complicate assessment of the results. The number of cells to be administered should be calculated by multiplying the expected clinical dose by the safety factors of the species and interindividual differences if possible. However, adequate consideration should be given to the possibility that the cells administered into animals may greatly affect the microenvironment at the administration site owing to the total volume itself, causing artifact changes. That is, the number of cells to be administered should be determined with the importance attached to the objective of tumorigenicity studies with subretinal transplantation, which is to investigate tumorigenicity of the final product (cells) in the microenvironment corresponding to the administration site in humans.

If retinal pigment epithelial cells (final product) are manufactured from multiple cell banks of human (allogeneic) iPS (-like) cells, and these cell banks have been established by the same method after HLA typing and confirmed to have quality attributes comparable to those of the raw material of the final product, tumorigenicity evaluation in a microenvironment corresponding to that at the administration site in humans should be performed for the final product manufactured from each cell bank in principle. Subretinal transplantation in immunodeficient animals is a representative approach for tumorigenicity studies of the final product. However, if a tumorigenicity profile of the final product in a microenvironment corresponding to that at the administration site in humans is considered to be rationally explained by data on the other quality attributes, tumorigenicity of the final product derived from each cell bank in human subretinal area can be estimated from data on the concerned quality attributes of the final product from the respective cell bank. (Reference data 9)

[2] Primary efficacy or performance studies of the final product

Expression of the function, durability of the action, and feasibility of clinical effects (Proof-of-Concept or POC) expected for the human (allogeneic) iPS (-like) cell processed product should be presented using animal models appropriate for the target disease to the extent technically possible and scientifically reasonable (Reference data 10).

If retinal pigment epithelial cells (final product) are manufactured from multiple cell banks of human (allogeneic) iPS (-like) cells, and these cell banks have been established by the same method after HLA typing and confirmed to have quality attributes comparable to those of the raw material of the final product, POC may be demonstrated using the final product manufactured from a representative bank.

[3] Others

For items deemed necessary and scientifically valid for clinical application, such as safety of a procedure for transplantation and acute local reactions after transplantation using the procedure, medium- or large-sized animals should be used according to the purpose if possible.

(5) Clinical studies (clinical trials)

[1] Indication

Diseases adversely affecting retinal pigment epithelium

Age-related macular degeneration, degenerative myopia, Stargardt disease, trauma, retinitis pigmentosa, etc.

[2] Systemic monitoring items

Subjects should undergo systemic screening for malignant tumor before transplantation wherever possible, because if a tumor is found outside the eye after transplantation, whether it is derived from the transplanted cells must be determined. Attention should be paid to tumor development, etc. for an appropriately pre-determined period of time after transplantation procedure.

[2] Assessment methods of transplantation treatment

Effects of the treatment of the disease subject to the guidance on evaluation can be evaluated mainly by 2 approaches presented in a) and b) below, anatomical and visual function-based assessments. Which approach should be used for endpoints at which time point should be specified as appropriate depending on the target disease and details of the treatment. For comparison, control data should be obtained from treatment results in past

reports or control groups used in these reports as appropriate according to the design of a clinical study. The clinical study may enroll, for example, patients who have not adequately responded to the conventional treatment (e.g., anti-VEGF therapy for age-related macular degeneration) or those who meet the certain criteria irrespective of response to the existing treatment. If the target disease is a type of the disease that progresses bilaterally such as hereditary degenerative disease, the untreated opposite eye should be used as a control.

The current assessment flow in the field of ophthalmology is provided below. Because ophthalmological examination technologies are rapidly advancing, assessment methods that are considered valid and appropriate for the study at that time should be used if possible.

a) Anatomical assessment

Ophthalmoscopy, diagnostic imaging (e.g., fluorescein angiography, optical coherence tomography), etc.

In recent years, diagnostic imaging technologies for ophthalmological examinations are remarkably advancing. For example, optical coherence tomography (OCT) is an examination technology highly useful and reliable in evaluating the protective effect on the retina over time objectively, because it is non-invasive and provides detailed and high-resolution cross-section images of the fundus, which give information about presence or absence of an active exudative lesion associated with age-related macular degeneration and actual quantitative status of residual photoreceptor cells including those affected by dry-type after treatment. Use of diagnostic imaging technologies such as OCT is the optimum approach to assessing survival and effectiveness of transplanted cells. For safety evaluation, fluorescein angiography and OCT are appropriate because these technologies are considered to provide data of the highest sensitivity, including information about rejection and tumorigenesis.

b) Visual function examination

Visual acuity, retinal sensitivity, perimetry, electrophysiological examinations, etc.

Pigment epithelial disorders in the macular area and secondary exudative age-related macular degeneration can be accompanied by exudative pathological conditions such as choroidal neovascularization, which gradually progress degeneration of photoreceptor cells in the overlying macular area. The visual function depends on the condition of photoreceptor cells. The primary objective of transplantation treatment is to prevent visual dysfunction (decreased visual acuity) of the macular area, which is inevitable after onset of these diseases, at the earliest possible time and to protect the remaining photoreceptor cell function by supplementing the healthy pigment epithelium to the macular area. Basically, restoration of the lost photoreceptor cells is impossible at the present time, and thus it does not suit the objective of this treatment.

Although central visual acuity is commonly used as an indicator representative of the visual function, it is affected by the position of remaining healthy visual cells in the central region. That is, the more photoreceptor cells closer to the central region remain, the better the visual acuity is kept. In age-related macular degeneration, etc., however, photoreceptor cells are lost in a random and disorder manner, but not in a concentric and uniform manner. To what extent photoreceptor cells remain in the macular area does not necessarily correlate with visual acuity. Visual functions based on subjective perception differ among individuals. (the following discrepancy cases actually occur: “I see numeric characters presented at a visual acuity test but cannot not perceive them”;

and “My visual acuity is numerically low, but I live more comfortably than generally thought.”)

Treatment given at the earlier stage of a disease can protect more photoreceptor cells closer to the central region and thus generally keep visual acuity unimpaired.

Treatment at the advanced stage of a disease, on the other hand, cannot be expected to improve visual acuity because photoreceptor cells in the central region have been already lost. However, if treatment protects intact photoreceptor cells surrounding the lesion, improvement such as a reduction in central scotoma (central blind spot) can be achieved.

Thus, visual function-based assessment should be comprehensively performed according to the stage of the target disease if possible, including retinal sensitivity or indicators related to response at a further local point in the macular area such as central vision and the extent, besides visual acuity in cases where assessment only based on visual acuity is considered inappropriate.

If the target disease is eligible for local analyses, electrophysiological examinations may be a favorable indicator as objective visual function tests.

If treatment is given to the dominant eye in patients with a bilateral eye disease, measures of vision-related quality of life (QOL) such as NEI VFQ-25 can be an indicator to assess visual functions (Reference data 12).

[4] Items that should be examined for allografting (use of immunosuppressants)

Immunosuppressants are supposed to be used pre- and post-allografting, but no guideline-recommended regimens are available to date. Informed consent to this matter should be obtained. Their use may be needed for a certain period of time pre- and post-allografting. Attention should be paid to complications associated with the extended use. Items that should be assessed for the above reason are listed below.

a) For Anatomical assessment, ophthalmoscopy and diagnostic imaging (e.g., fluorescein angiography, optical coherence tomography, fundus autofluorescence imaging) should be performed to capture changes over a period of time. Attention should be paid to not only the transplantation site but also color of the entire fundus and inflammatory or exudative changes in the eye including the vitreous body and anterior chamber of the retina.
b) For visual function-based assessment, visual acuity, retinal sensitivity, perimetry, electrophysiological examinations, etc., should be performed. Special attention should be paid to cases where the test results indicate worsening despite previously showing an improving trend after transplantation.
c) Monitoring the recipient for systemic complications associated with systemic administration of immunosuppressants and periodic blood sampling should be performed.

6. Reference data

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