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GUIDELINE ON CLINICAL INVESTIGATION OF IMMUNOSUPPRESSANTS FOR SOLID ORGAN TRANSPLANTATION

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GUIDELINE ON CLINICAL INVESTIGATION OF IMMUNOSUPPRESSANTS FOR SOLID ORGAN TRANSPLANTATION

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EXECUTIVE SUMMARY

The aim of this guideline is to provide guidance on the clinical development of compounds for the prevention and treatment of allograft rejection in solid organ transplantation.

The immune system is vital for the human body and immunosuppression in organ transplantation should be as selective as possible, to minimise the risk of over-immunosuppression which can cause increased risks of infections and malignancies. Many problems exist in currently approved regimens: Treatments are often very complex, e.g. quadruple immunosuppression, and vary over time for each patient. This complexity also increases the risk for low patient compliance. Therapeutic margins can be very narrow and there are considerable risks of over- as well as of under immunosuppression. The pharmacokinetic interaction potential is high and causes problems (decreased efficacy, increased toxicity) as transplant patients are often on multiple other drugs. Many widely used immunosuppressive protocols in transplants performed in low numbers, i.e. lung, bowel and islet transplantation, are not approved for that indication.

Different treatment settings and modalities, such as type of organ transplantation (renal, liver, heart, lung, etc.,) type of therapy (induction, initial, maintenance, tolerance induction), type of allograft rejection (hyperacute, acute, subacute, "chronic", and/or (steroid) resistant), and type of pathophysiology (cellular or humoral type of rejection) are distinguished. Many different immunosuppressive drugs and a number of different combinations are currently available and new agents are under development. Other treatment concepts that are explored include steroid withdrawal or total avoidance of steroids, drug minimisation and induction of tolerance.

This document considers these circumstances and provides guidance for proper development of new immunosuppressant for solid organ transplantation. Potential claims provided reflect principal aims of management of transplanted allograft with immunosuppressant. Baseline subject characteristics and selection criteria of subjects considers immunological and global transplantation risk assessment; both for donor/transplant and recipient. Primary efficacy criteria are provided in general terms and are seen as constructed by composed and/or co-primary endpoints only. Guidance on pharmacokinetic and pharmacodynamic investigations reflects mainly specific pathophysiology during peri-transplantation period, co-therapies, and monitoring strategies. Exploratory trials should reflect concepts of immunosuppression for investigated agent and base strong rationale for confirmative investigations. Guidance on confirmatory trials is provided mainly for major transplantation areas, such as renal, liver, heart, lung and pancreas transplantation. Specific areas with limited experience gathered up till now, such as development of minor transplantation areas as well as choice of non-approved comparators are recommended to be guided by European regulatory advice procedures. Special issues in paediatric, elderly population and in case of certain infections during peri-transplantation period are advised to be investigated by tailored trials. Clinical safety investigation should reflect certain essential characteristics of immunosuppression in solid organ transplantation, such as life-long lasting treatment in a population with extensive co-morbidity. Specific factors to be considered include proper time for assessment of infectogenic and cancerogenic potential, risk of premature death due to primary disease and overlapping safety signals.

This document should be conceived as general guidance, and should be read in conjunction with other EU and ICH guidelines that apply to the subject (see Section 3 "Legal basis").

Due to the dynamics of the field, frequent revisions and amendments are foreseen.

1. INTRODUCTION

When an organ or tissue from one individual is transplanted into a genetically non-identical other individual, a series of cellular and molecular events are initiated. If no action is taken, this will result in rejection of the graft. This response involves reperfusion injury, innate and adaptive immune response and therefore a variety of partly overlapping pathophysiological processes. The precise molecular nature of alloantigen and host interaction and of effector mechanisms is not known. A number of immune cells, such as T-, B- and NK- cells, macrophages and dendritic cells, generate a number of cellular and humoral immunological events that result in allograft rejection. A rejection can be hyperacute, acute, subacute, or "chronic". Since T cells play a major role in adaptive immunity, the primary focus in the development of immunosuppressive drugs has traditionally been directed against them.

The diagnosis of allograft rejection relies heavily on adequate diagnostic methods, among which the ultrasound-guided transplant biopsy for kidney transplants, with histological grading according to the Banff criteria, is the reference method. Additionally, although some biochemical tests suggest hepatic allograft damage, the standard for defining rejection remains based on morphologic findings also. Independent and blinded evaluation of transplant biopsies according to these accepted criteria is crucial for clinical studies of immunosuppressive agents.

1.1 Epidemiology

End-stage organ failure is a public health concern with few treatment alternatives, transplantation often being the best option for vital organs: kidney, liver, heart and lungs. Over 1 million people worldwide have undergone successful organ transplantation.

The annual transplantation rate in Europe is 15 000 kidneys (2000 from living donors), 5500 livers, 700 pancreases, 2000 hearts and 900 lungs (100 combined heart and lung). Numbers and rates per million population varies widely within the European Union, from just few to 50 for kidney, 0 to 25 for liver, 0 to 0.4 for pancreas (up to 3 for kidney-pancreas), 0 to 7 for heart (including heart-lung) and 0 to 5.6 for lung (including heart-lung) transplantations. Worldwide, the gap between the need for available organs and number of recipients increases constantly. As consequence, acceptance of extended criteria donors, with the consequences of increased risk of unfavourable transplantation outcome becomes an increasing reality.

One year patient survival exceeds 95% in kidney, 85% in liver, 95% in pancreas, and is about 85-90% in heart and 73-83% in lung transplantation. One year graft survival now exceeds 85% in kidney, 80% in liver and is 64-83% in pancreas transplantation. Five years survival rates for most organ transplant programmes exceed the ranges from 50 to a 70%.

The incidence of rejection depends on many internal factors and type of transplantation. Acute rejection varies widely in different materials. Numbers between 10 and 40% have been reported during the first 12 months in kidney, about 20-50% in liver, 10-40% in pancreas, about 50% in lung and 50-80% during first 6 months in heart transplantation. Usually, acute humoral rejection comprises a minimal proportion of acute rejections. As an example in heart transplantation acute humoral rejection occurs in 7% of patients compared with an incidence of 40-70% of acute cellular rejections. The incidence of “chronic rejection” varies very much in different patient materials, depending on type of organ transplanted, period studied and definition of diagnosis. Figures from less than 10% in liver to well over 50% in heart and lung transplantation have been reported.

1.2 Treatment

Organ transplantation has been an area of rapid development during more than four decades. This has been achieved through a combination of progresses within the fields of surgery, immunology, drug development and general standards of care where progress in the treatment and prophylaxis of infectious diseases has been of major importance for clinical outcome. Since short term patient and graft survival has improved and the number of graft failures attributed to acute rejections has decreased, factors other than acute rejection now tend to account for more of the long term morbidity and mortality: recurrence of original disease, chronic progressive allograft dysfunction (CAD) (i.e. long-term deterioration of the graft, formerly called chronic rejection). The incidence of cardiovascular disease as well as of malignancy in transplant recipients is high and many transplant recipients die with a functioning graft.

The aim of immunosuppression in clinical practice is to control an undesirable immune response while avoiding, if possible, the complications of immunodeficiency. The effect can be achieved by ablation (i.e. irreversibly damaging immune tissue); by altering lymphocyte location and traffic; by altering lymphocyte or dendritic cell function; or by affecting lymphokines. These interventions may be physical (e.g. by irradiation, plasmapheresis, photopheresis) or pharmacological.

Current immunosuppressive pharmacological therapies can be classified according to mechanism of action.

- Glucocorticosteroids (e.g., prednisolone)
- Immunophilin binding agents: calcineurin inhibitors (e.g., cyclosporine, tacrolimus) or mTOR inhibitors (e.g., sirolimus, everolimus)

- Inhibitors of de novo nucleotide synthesis: purine synthesis (e.g., mycophenolic acid, mizoribine), pyrimidine synthesis (e.g., leflunomide)
- Antimetabolites: (e.g., azathioprine)
- Antibodies: antibodies against immune proteins (e.g., polyclonal ALG, ATG IL-2R targeted, anti-CD25 and anti-CD3 monoclonal), intravenous immunoglobulin (e.g., IVIG).

In this context it is acknowledged that use of some immunosuppressive drugs, e. g leflunomide and cyclophosphamide, reflects evidence based clinical experience only, that region-specific preferences are common and that all this has an impact on the feasibility of conducting well-controlled clinical studies.

Clinically, pharmacological immunosuppression can be classified as follows (see 5 "Definitions"):

- **Prevention of graft rejection:** induction, initial and maintenance therapy.
    - **Induction therapy** usually means the use of ATG, ALG, basiliximab, daclizumab, or, rarely, muromonab-CD3.
    - **Initial therapy** is often "triple therapy", in which a calcineurin inhibitor is used as basal immunosuppressive agent in combination with corticosteroid and mycofenolate mofetil (or azathioprine or sirolimus). In some regions, dual therapy dominates.
    - **Maintenance therapy** is often identical to initial therapy but at:
        - Reduced dosage *or*
        - Reduced number of immunosuppressives, e.g.:
            - "Dual therapy" that can be a switch from "triple therapy" after discontinuation of one of the agents used in the initial immunosuppression
            - Monotherapy, usually with the calcineurin inhibitor initially used as basal immunosuppressive in renal or liver transplantation.
- **Acute rejection therapy** could be achieved by:
    - Adjustment and increase of (temporarily or permanently) maintenance therapy
    - Short courses of high-dose corticosteroids (one or several doses), sometimes followed by temporarily or permanently increased doses of oral corticosteroids
    - For corticosteroid resistant acute rejection: either ALG, ATG, muromonab-CD3 *or* switching to another basal immunosuppressive agent. Experience-based clinical use of certain immunosuppressants (such as rituximab and alemtuzumab) is common in corticosteroid resistant rejection.
    - Humoral acute rejection could be treated additionally with high doses of IVIG or with plasmapheresis.
- **Treatment of CAD.** At present, no approved therapy exists for CAD. Many different approaches have been tested but are not sufficiently supported by data.

2. SCOPE

The aim of the guideline is to provide guidance on the conduct of clinical studies for solid organ transplantation by defining treatment goals, study designs, outcome measures and data analysis for new immunosuppressive products developed to prevent and treat solid organ allograft rejection.

The main goal is expected to be achieved by relatively selective immunosuppressant regimen that should pose an optimal balance between beneficial immunosuppression of immune reaction leading to rejection on one hand side, and over-immunosuppression which can cause increased risks of infections and malignancies on the other.

3. LEGAL BASIS

This document should be read in conjunction with Directive 2001/83/EC (as amended) and relevant provisions of Regulation (EC) No 141/2000 on orphan medicinal products as well as Regulation (EC) No 726/2004 regarding granting conditional marketing authorisation

In addition, relevant CHMP Guidelines should be taken into account. These include but are not limited to:

- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4)
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9)
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10)
- Points to Consider on Adjustment for Baseline Covariates – CPMP/EWP/2863/99
- Points to consider on Missing data – CPMP/EWP/177/99
- The Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1A)
- Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7)
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 ICH11)
- Pharmacokinetic studies in man - (3CC3A)
- Choice of the Non-Inferiority margin - CPMP/EWP/2158/99
- Points to Consider on Multiplicity Issues in Clinical Trials - CPMP/EWP/908/99

4. MAIN GUIDELINE TEXT

4.1 Potential claims

The principal aims of management of transplanted allograft with immunosuppressant and thus, potential indications are (see Section 5 “Definitions”):

- Induction prophylaxis
- Initial and/or maintenance prophylaxis
- Acute rejection treatment

Induction prophylaxis could have the purpose to:

- Delay the initiation of nephrotoxic immunosuppressant, such as calcineurin inhibitors in renal transplantation or, e.g., in case of oliguria/hepato-renal syndrome in liver transplantation;
- Allow the minimisation of the toxic potential of other immunosuppressive drugs (e.g., minimisation or withdrawal of maintenance corticosteroids, calcineurin inhibitors)
- Affect new pathophysiological components of immune response (such as resolution of humoral rejection, tolerance induction).

It is not expected that these additional claims would be an independent indication or base a part of the indication. Additional clinical benefits could be reflected in Section 5.1 of SPC.

Initial and maintenance prophylaxis indications may be combined into one indication (namely “acute rejection prophylaxis”). Precise description of conditions should be provided in Sections 4.1 and 4.2 of SPC.

Switching from one maintenance prophylaxis regimen to another after a period of successful prevention, e.g. in order to improve safety, may constitute a clinically relevant aim to be reflected in Sections 4.1, 4.2 and/or 5.1 of SPC.

Concept of primary or secondary type of prophylaxis could be considered but is not expected to be included as a claim.

Acute rejection treatment indication should be further specified with information gathered regarding suitability in case of resistance to conventional anti-rejection therapies and regarding suitability in case of first or following/multiple rejections. In case of insufficient information for generalisation in Section 4.1 of the SPC, information gathered during development should be reflected in Sections 4.4 and/or 5.1 of the SPC.

CAD reflects progressive graft dysfunction against a complex immunological and non-immunological pathophysiological background. Indication of treatment and/or prophylaxis of CAD can not be granted as an indication unless specifically defined and investigated.

4.2 Subject characteristics and selection of subjects

It is fully acknowledged that there is no consensus as regards the importance of individual risk factors and how to define cut-offs for increased risk, but the following factors are frequently taken into account: previous early graft loss due to immunological factors, re-transplantation, panel reactive antibody (PRA) level, and presence of auto-antibodies, HLA mismatch, and original disease.

Best attempts should be undertaken to define individual's **immunological risk** at baseline, e.g. according to the following categories: low/medium/high or elevated/non-elevated immunological risk group.

Transplantation outcome is influenced not only by immunological factors but also by surgery and co-morbidity. Therefore the development of reasonably validated scales for the assessment of **global transplantation risk** would be welcomed.

Patient inclusion in clinical studies should reflect the intended target population, but may be restricted, at least in initial studies, e.g. based on immunological risk if properly justified.

Baseline characteristics

The study population should reflect the target population and should be characterised at baseline, in respect of immunological and infectious factors, different surgical and transplantation type procedures, co-morbidity and co-medication used. Documentation of the following data among others depending on the organ transplantation is required:

For recipients

- Age, gender, body mass index (BMI) and ethnicity
- Primary diagnosis
- Duration of severe/terminal organ failure and type of treatment modalities (such as type and duration of pre-transplant dialysis)
- The level of PRA, cold and warm ischemia time, known mismatches with influence on transplantation outcome, e.g. HLA mismatches, gender mismatch, AB0 mismatch, CMV donor/recipient mismatch and other risk factors
- Co-morbid disorders and risk factors with known influence on transplantation outcome such as hypertension, diabetes, infections, hyperlipidaemia with disease complications and evaluation of treatment adequacy at baseline
- Baseline serology for risk factors for transplantation outcome may include CMV, HBV, HCV, EBV, HIV, polyoma virus, HSV8
- The number of previous transplantations and prior and concomitant therapies
- Transplantation type and procedure related risk factors (such as size match in heart transplantation, pre-emptive type of surgery, renal insufficiency, preoperative invasive ventilation)
- Post-transplant surgical complications, when relevant and other general surgical risk factors.

For acute rejection treatment, additionally:

- Acute rejection type as per selected definition and methodology of diagnosis of acute rejection, including histological definition of rejection according to the Banff criteria

- Previously used immunosuppression; resistance

For donor and transplant

- Donor type [cadaveric (non heart beating donor (NHBD or not) or living], number of HLA mismatches, demographics (age, gender, and race) and functional evaluation of the organ in the donor Cause of death for cadaveric donor
- Serology positive for risk factors (such as HBV, HCV, CMV, EBV, HIV, HSV8 and other active infections)
- Donor hyperglycaemia, hypoxia, haemodynamic instability or acidosis or prolonged oligo- or anuria
- Organ specific risk factors, e.g. cold ischemic time, complicated transplant vascular anatomy; organ atherosclerosis, left ventricular hypertrophy or ventricular dysfunction in heart transplantation; liver steatosis for liver transplantation.

Transplanted patients are likely to have several concomitant diseases (such as diabetes, hyperlipidaemia, hypertension, obesity or ischemic heart disease) with possible negative impact on clinical outcome. Restriction of target population may increase precision of study result but diminishes generalization of study's findings to a broader population.

Enrolment of patients in clinical studies is partly governed by region specific transplantation policies and this, together with investigator/patient driven selection, may lead to region-related imbalances, e.g. as regards global transplantation risk to be taken into account in the analysis of treatment results.

Co-medication: All products taken must be documented and medicinal products that could affect the results during the study must be predefined and excluded if feasible.

4.3 Methods to assess efficacy

4.3.1 Definition of the primary endpoints

The ultimate aims of solid organ transplantation are improved survival and improved quality of life while the goals of development of new immunosuppressants are:

- to improve efficacy and/or safety outcomes of well-established immunosuppressive concepts
- to introduce new concepts of treatment (such as tolerance induction and exclusion of maintenance therapy) replacing well-established concepts

and could be sought for induction prophylaxis, initial and/or maintenance prophylaxis, acute rejection treatment.

The primary efficacy endpoint for induction, initial and/or maintenance prophylaxis (**primary prophylaxis**) should be efficacy failure rate using a composite endpoint consisting of:

a) patient death

b) graft failure (defined by clear-cut and discrete criteria, such as permanent return to pre-transplantation treatment modality for a defined period of time e.g. return to dialysis for at least 4–6 weeks or more, renal re-transplantation, nephrectomy in kidney transplantation)

c) biopsy confirmed acute rejection BCAR

d) graft dysfunction (defined by clear-cut and discrete criteria) for at least kidneys, lungs and hearts

Alternatively, and in order to increase the sensitivity of clinical studies, co-primary endpoints may be used: the composite of a) to c) plus d) as a continuous variable.

For **secondary prophylaxis,** the same endpoints as for primary prophylaxis may be used but with emphasis on second or subsequent BCAR episodes.

For **acute rejection,** the selected primary endpoint should capture: resolved first biopsy-confirmed acute rejection episode, second BCAR episode, patient graft survival and patient survival. Rejection-free graft and patient survival might be appropriate, estimated from time of randomisation.

In case of failure to resolve the initial rejection episode, rejection-free survival is thus 0 days. These endpoints are applicable to both treatment naïve cases and to cases resistant to rejection therapy.

The primary efficacy endpoint for **CAD** treatment should capture preservation of transplant organ function, graft and patient survival.

4.3.2 Definition of secondary endpoints

The following secondary endpoints in solid organ transplantation should always be reported:

- Graft function at various time points e.g. 6, 12 months, and 3, 5 years
- Graft survival at various time points e.g. 6, 12 months, and 3, 5 years, with reasons for graft failure
- Patient survival at various time points e.g. 6, 12 months, and 3, 5 years, with reasons for death
- Incidence and/or time to biopsy-proven first acute rejection

Other frequently reported endpoints include:

- Incidence and/or time to biopsy-proven second acute rejection
- Incidence and/or time to clinically treated acute rejection episodes
- Incidence and/or time to first glucocorticosteroid resistant rejection
- Incidence of graft loss preceded by a rejection episode
- Incidence of graft loss preceded by a rejection episode treated with antibody therapy
- Severity of acute rejection
- Incidence of patients experiencing multiple rejection episodes
- Incidence of treatment failure (defined as need to stop the experimental compound)
- Incidence of crossover for treatment failure
- Incidence of delayed graft function (DGF)
- Cumulative dose of corticosteroids and/or use of anti-lymphocyte antibody therapy for treatment of rejection
- CMV infections during the first six months and in renal transplants, activation of BK-virus
- Incidence, type, and severity of associated infections
- Incidence and type of associated malignancies
- Quality of life (QoL) outcome.

Rejection and severity of rejection should be measured by validated measurements and scales and like the Banff Grade $\geq$ 1 for renal transplant rejection or other internationally well established scales in other transplantations. Graft function should be measured according to well validated variables, e.g. GFR measured by iohexol clearance or calculated according to a well validated formula.

In case claims related to a secondary endpoint are foreseen, care should be taken to avoid multiplicity.

4.4 Strategy and design of clinical trials

4.4.1 Pharmacokinetics

The pharmacokinetics of the experimental medicinal product should be documented in accordance with relevant guidelines. The immediate post-transplantation period is characterised by unstable renal and/or hepatic function, leading to very variable absorption, distribution and/or elimination of medicines. External drainage of bile in the early postoperative phase after liver transplantation could reduce the entero-hepatic circulation and thus change systemic exposure of active immunosuppressants. Altogether, pharmacokinetic studies during unstable periods after transplantation are mandatory and dosing proposals during these periods should be justified.

As a number of immunosuppressive medicinal products are often administered concomitantly and as it might be problematic to foresee interactions solely based on mechanistic thinking, interaction studies for main immunosuppressives are recommended, even if PK interactions are considered unlikely. In addition, population PK studies may be informative.

4.4.2 Pharmacodynamics

Dosing of immunosuppressants directly after organ transplantation is based mainly on the need for intense and constant immunosuppression. Valid pharmacodynamic markers for immunosuppression post-transplantation are currently not available, but would be of great value as such markers could improve clinical monitoring practice. Future developments, such as immunotolerance induction, may generate a need for new valid biomarkers.

Current practice recognises a possibility of decreased need for immunosuppression and therefore drug exposure with time after transplantation. Clinical studies aiming to investigate the development of immunological tolerance are encouraged.

Very often, immunosuppressants used in transplantation are subject to high inter-individual pharmacokinetic variability. Immunosuppressants often have a narrow therapeutic window and efficacy and safety PK/PD studies are essential, with evident implications for clinical safety and efficacy. Currently tests predictive of over- and under- immunosuppression are under development and when reasonably validated, their inclusion at least in exploratory studies is encouraged.

Need for vigorous PK and/or PD monitoring strategy should be evaluated prospectively. Suitable routine clinical practice monitoring methods and parameters (such as trough blood concentration level measurements) should be validated before marketing authorisation.

4.4.3 Therapeutic studies

a. Exploratory trials

The rationale for dose-finding should be defined prospectively, taking into consideration developed concepts of immunosuppression for the investigated agent (such as need for time-dependent activity, need for loading dose, time-dependency in need for exposure of immunosuppressant). Dose-ranging studies should be preferably performed in a controlled, parallel fixed-dose design, using at least three dosages. It is acknowledged that for monoclonal antibodies targeting cells in the peripheral circulation, dose finding may be simplified. Safe and effective therapeutic margin should be preliminarily established before confirmatory trials are initiated. Use of pharmacodynamic markers are encouraged in order to increase the sensitivity of these exploratory studies, but, e.g. time to rejection in combination with search for signs of over-immunosuppression provide more robust data. These trials are often first conducted in low risk patients assigned to undergo renal transplantation. Whether further dose-finding studies are needed prior to the initiation of confirmatory studies in other transplantation areas should be defined in relation to available data for the experimental compound and the class of compounds.

Parallel group, randomised, placebo-controlled (when feasible) add-on trials are recommended, where background therapy should be a transplantation regimen acceptable from a clinical perspective.

Since immunosuppressive therapy often has a narrow therapeutic window, concentration-controlled therapy is advised when indicated.

Primary prophylaxis of acute rejection. The majority of first acute rejections occur during first 6 to 12 weeks and current practice dictates increased need for immunosuppression during the first 12 to 24 weeks after transplantation. While efficacy data might be informative already after 12 weeks, the need to assess signs of over-immunosuppression implies that exploratory trials for at least 24 weeks for **induction** and **initial** prophylaxis are needed. If exploratory trials for **maintenance** prophylaxis are undertaken, the study duration should be at least 12 months. Patient and graft survival should be followed for at least 1 year.

Secondary prophylaxis of acute rejection could be estimated by second BCAR within a reasonable time frame (e.g., at 24 weeks for renal transplantation) with or without other efficacy endpoints, severity of second BCAR, incidence and time to first corticosteroid resistant BCAR, incidence of chronic rejection and treatment failure, patient and graft survival.

Treatment of acute rejection. Successfully treated acute rejection episodes usually resolve within 4 weeks. This implies that exploratory trials of at least 4 weeks duration are required. Additionally, patient and graft survival monitoring should be extended to at least 1 year.

Regular visits and proper diagnostic tools (including protocol biopsies when crucial, e.g. in case of heart transplantation, blind assessment, external committees etc.) should be scheduled to verify absence of rejection throughout the trials.

b. Confirmatory trials

New agents are introduced with the hope of improved prevention of allograft loss or acute rejection treatment or better safety, etc. Organ specific indications are foreseen also for the future, requiring separate confirmatory studies. More investigations in the area of CAD are clearly needed.

Most clinical trials are designed to compare the efficacy or safety of a new regimen with a well-established standard therapy. Comparative trials should be designed as randomised, parallel group studies according to the aims of product development: (A) to substitute one or several therapeutic components of well-established immunosuppressive regimens to improve efficacy, safety or compliance or (B) as add-on to improve efficacy of an approved regimen, or (C) to introduce new concepts of treatment replacing current well established therapy regimen.

From a regulatory perspective, the experience is limited in certain areas such as minor transplantation indications (e.g. small intestine transplants, therapies for steroid resistant acute rejections, protocols for induction of immune tolerance) With respect to these areas, it is advisable to reach European regulatory advice with respect to study design prior to the initiation of confirmatory studies.

Choice of comparator

The choice of comparator(s) and dosage will depend on the sought indication, type of transplantation and risk of rejection. If an approved regimen already exists, active comparison with that regiment is necessary. In the absence of approved regimen for a given indication, best standard practice should be employed. Especially for the treatment of steroid-resistant rejection and some minor transplantation indication, the problems to identify a reference regimen are acknowledged. With respect to the choice of non-approved comparator, it is advisable to reach European regulatory advice with respect to the choice of comparator prior to the initiation of confirmatory studies.

Study duration

For **induction prophylaxis** the study duration should normally be 12 months in order to fully capture the effects of induction therapy on the safety and efficacy of the primary prophylaxis regimen.

Usually **initial** prophylaxis reflects the early post-transplantation period with higher need for immunosuppressive exposure (up to 12-24 weeks) while **maintenance** prophylaxis should be investigated during a period starting from 2nd to 3rd months and lasting at least 12 months after transplantation.

Primary or secondary prophylaxis of acute rejection: A minimum of 12 months should be considered for either primary or secondary type of prevention studies.

c. Methodological considerations

Known and unknown factors besides the actual treatment might impact study results. Immunological risk and region are factors often considered to be of major importance in the design of clinical studies. In addition, organ procurement/preservation/preparation techniques, donor/recipient choice, surgical technique and management as well as transplantation type are of importance. Procedure-related and treatment-related risk factors include

- in heart transplantation: ventricular assist devices or ventilator use, hyperdynamic circulation
- in renal transplantation: hyperdynamic circulation and early post-transplantation oliguria hyperfiltration, delayed graft function, heavy proteinuria
- in liver transplantation: preservation injury, early post-transplantation oliguria
- in lung transplantation: bronchial anastomotic complications and pulmonary vascular complications, significant ischemia reperfusion injury.

Such risk factors should be reported and the most important factors should be identified beforehand and taken into consideration by proper stratification of the randomisation and / or inclusion of these factors into the analysis model.

Patient and graft survival is a function of baseline and treatment-related factors. Since graft dysfunction/survival depends on the continued optimal functioning of the graft, the early recognition, prevention, and management of graft dysfunction is emphasized. Methods such as properly scheduled visits at the transplantation centre, phone monitoring, and patients self monitoring should be employed.

Graft biopsies are of major importance for the proper management, e.g., of heart transplantation, but a too demanding study protocol may in other areas, such as renal or lung, lead to non-representative centre and patient inclusion. The benefit of protocol biopsies therefore should always be weighed against possibly negative impact on the external validity of the study. Long-term management of complications should be focused on prevention and management of both immune and non-immune complications.

4.5 Studies in special populations

Pharmacokinetic and dedicated efficacy/safety studies in children should be undertaken to address specific paediatric issues such as proper extrapolation of adult dosage to children, thrombotic complications, and recurrence of original disease or atypical haemolytic-uraemic syndrome. Strategies to minimize effects on growth and development after transplantation are especially important and should be evaluated if applicable. For adolescents, PK/PD studies are sufficient.

Age is important unfavourable risk factors in transplantation. As age of recipients is increasing, confirmatory studies should reflect this and a sufficient number of elderly, e.g. above 65 years of age, should be included. The influence of specific risk factors should be investigated (such as accurate diagnosis and treatment of cardiovascular disease, diabetes mellitus, bone disease and malignancies).

Patients with specific infections (e.g., HIV, HCV, or TB) may need to have special peri-transplantation management protocols considering negative impact of immunosuppression for allograft rejection, specific co-medication regimens. In these cases note must be taken of updated, generally acknowledged clinical treatment guidelines.

4.6 Clinical safety evaluation

4.6.1 General considerations

Safety is normally assessed based on treatment-emergent adverse events, the results of routine clinical laboratory tests, and vital sign measurements at time intervals relevant for particular transplantation type and type of medicinal product under evaluation.

Subjects who undergo solid organ transplantation are required to receive life-long (or at least, long-term) treatment with immunosuppressive medicinal products. Data obtained from long-term studies are therefore essential. Subjects included in pivotal clinical trials for transplantation should therefore reflect the target clinical population, a population with extensive co-morbidity.

4.6.2 Specific adverse events

Risk of infection is a function of time and degree of immunosuppression. As immunosuppression is usually at its highest level during the first 6 months after transplantation, this is also the peak period for bacterial, fungal, and viral infections in patients.

The risk of developing several types of malignancies is increased in organ transplant recipients. The majority of de novo malignancies in transplant recipients appear during a time period of not less than 10 years. This period is needed for safety studies regarding claim of comparative clinical carcinogenic potential.

The risk of premature deaths due to the primary disease (e.g. diabetes) should be considered carefully and concomitant therapy should be optimised at baseline.

Overlapping safety signals (such as de novo diabetes, nephrotoxicity cases, cardiovascular, or other known adverse effects of concomitant immunosuppressants) should be specifically investigated and documented.

5. DEFINITIONS

Biopsy-confirmed acute rejection (BCAR) is a rejection defined by well established histological definition and rating system (such as Banff Grade $\geq$ 1 for renal transplantation) and confirmed by blinded methodology by independent investigator/committee).

Induction prophylaxis (prevention) (induction therapy) is a course of intensive immune suppression for about 2 weeks immediately post transplantation and is often started immediately pre-operatively with the aim of "switching off" the immune system after transplantation.

Initial prophylaxis (prevention) (initial therapy) is the treatment given to all recipients (except where donor is an identical twin) for 0-3 (sometimes up to 6) months after transplantation.

Maintenance prophylaxis (prevention) (maintenance therapy) is the treatment that patients receive long-term, throughout the duration of allograft survival.

Acute rejection treatment is the therapy following acute rejection and especially following multiple rejection episodes.

Resistant rejection treatment is a therapy of acute rejection resistant to high dose glucocorticosteroids during a defined period of time.

Chronic allograft dysfunction (CAD) (also called **chronic rejection, biopsy confirmed chronic rejection, BCCR**) is a long-term deterioration of the graft function. It is usually a gradual process, caused by immunological and non immunological causes (such as ischemia, drug toxicity, recurrence of original disease and other causes) although both the time of onset and the rate of progression vary. CAD may develop as early as within few months of the transplant or it may emerge after several years. The course is generally unremitting and ultimately leads to total loss of graft function.

Expanded criteria donor: Deceased donor who falls outside the standard criteria used to determine donor suitability.

Triple therapy: Immune suppression regimen with three immunosuppressants, usually a calcineurin inhibitor, an antiproliferative agent plus a corticosteroid.

Dual therapy: Usually a calcineurin inhibitor or an antiproliferative agent plus a corticosteroid.

Quadruple therapy: Usually: (1) induction therapy (prophylaxis); (2) calcineurin inhibitor; (3) an antiproliferative agent and (4) a corticosteroid.

Monotherapy: Usually a calcineurin inhibitor.

6. REFERENCES (scientific and/or legal)

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