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IPRP Reflection Paper

General Principles to Address the Nature and Duration of Follow-up for Subjects of Clinical Trials Using Cell Therapy Products

1. Position Statement

The International Pharmaceutical Regulators Forum Programme (IPRP) Cell Therapy Working Group (CTWG) has prepared this reflection paper to provide their perspectives on factors to be considered when deciding on the nature and duration of clinical follow-up for patients receiving cell therapy products. The recommendations stated in this paper are applicable to monitoring patients for safety only. Monitoring for efficacy depends on additional factors that are not discussed below. Furthermore, this document does not address clinical follow-up for patients who have received genetically modified cells.

Unlike typical pharmaceuticals, cell therapy products are complex and pose potential safety risks due to unique specific characteristics of the cells, the final product, the disease for which it is intended, and the context in which the cells will be used.

2. Executive Summary

This reflection paper presents principles regarding the factors to be taken into consideration, on a product-by-product basis, when determining the length and type of follow-up of recipients of cell therapies. In addition to being tailored to characteristics of the study population, such as age and immune competency, the follow-up plan needs to be indication-specific and product-specific. The contents of this paper will assist sponsors of cell therapy clinical trials in planning an adequate follow-up of subjects who have received a cell therapy product. The potential for long-term benefits, which may be accompanied by long-term risks, of cell therapies is partly attributable to their persistence, relative to small molecule therapeutics. Follow-up plans need to consider the time – in days, months or years – that a product is projected to persist in recipients, requiring that recipients of cell therapies be followed longer than the recipients of relatively short-acting treatments. Other factors should be considered, such as whether the cells are derived from allogeneic or autologous sources and the relative challenges they pose. For example, autologous cells may be more difficult to identify as causal agents of a tumor. Posology (including site and route of administration, speed of administration, number of doses and the dose itself), the type of cell and the differentiation state of that cell, influence of manufacturing altering the quality and stability of a cell line, cell adhesion promoting survival, growth and differentiation, all may affect the persistence of the cellular product and contribute to determining the length of follow-up. Higher cell number and size may require close monitoring in the period immediately after administration, as there may be risk for embolization. Other factors that contribute to the follow-up decision are prior experience and knowledge as well as type of procedures and concomitant therapies. One must, however, also remember the benefits and that all of these elements contribute to the benefit/risk balance of cell therapies in the context of the severity and

unmet need of each disease treated. Sponsors are encouraged to discuss their long-term monitoring plans with regulatory authorities, and may consider the regulatory acceptability of such plans for risk mitigation systems and post-marketing surveillance.

3. BACKGROUND

The IPRP, formerly known as the (IPRF)[1], CTWG has its roots in the discussions that began in 2011 at the ICH Regulators Forum. The goal of the Regulators Forum was to identify possible areas of convergence in regulatory practice for cell and tissue-based therapies. When the IPRF was formed in 2013, the CTWG began to focus on defining principles to guide the use of cell therapy products in clinical practice and clinical research. Because of the particular, possibly long-term properties of cell therapy products, the CTWG conducted a member survey that identified factors to consider in determining the nature and duration of clinical follow-up for subjects or patients who receive cell therapies. The principles described below generally apply to monitoring of subjects throughout the course of clinical development and beyond. While the survey focused on monitoring for the purpose of assessing safety, many of the principles described below are also relevant to monitoring for efficacy.

Cell therapy products may persist in the recipients for days, months, or years. These prolonged exposures, unlike the duration of exposure to most small molecule therapeutics, carry the potential for both long-term benefits and long-term risks. The effects of a cell therapy product might also evolve over time (e.g., stem cell products that proliferate and differentiate). Clinical development and use of a product requires follow-up (i.e., monitoring) of product recipients for both expected and unexpected adverse events, to mitigate the risks to the recipients as well as to inform future development and use of the product. Because of the potential for prolonged cell persistence and activity, recipients of cell therapy products may need longer follow-up than for relatively short-acting small molecule therapeutics. The nature and duration of follow-up should be carefully considered to ensure the safety of the recipients of the product. This prolonged persistence may also substantially influence the expense and feasibility of drug development and clinical practice. When making these decisions, safety directives associated with already existing cell transplant programs should be considered, and could be adapted to individual situations in the context of current practice. However, there are no current regulatory opinion papers on how to consider the nature and duration of follow-up specifically for subjects who receive cell therapy products.

4. FACTORS INFLUENCING THE NATURE AND DURATION OF FOLLOW-UP

The CTWG discussed which factors are most important in determining the nature and duration of follow-up. These factors are product-specific and case-specific and include (but are not limited to) characteristics of the cell product and its manufacturing process (see 4.1), characteristics of the study population (see 4.2), posology (see 4.3), procedures or concomitant therapies (see 4.4), and previous experience and existing knowledge with the cell product or related products (see 4.5).

[1] The International Pharmaceutical Regulators Forum (IPRF) merged with the International Generic Drug Regulators Programme (IGDRP) in January, 2018 to form the International Pharmaceutical Regulators Programme (IPRP).

In general, long-term monitoring, if necessary, might not need to be as detailed as the safety monitoring in the initial part of a clinical trial. Such long-term monitoring may assess cell survival and persistence, proliferation, migration, and differentiation. From the standpoint of the safety of the product, long-term monitoring usually focuses on patient survival and serious adverse events (e.g., hematologic, immunologic, neurologic, or oncologic events). Completion of long-term monitoring of clinical trial subjects is often not necessary prior to initiating subsequent clinical trials or submitting a marketing authorization application. However, some waiting period is usually required before moving from early studies to more advanced studies. This period of observation provides information on what clinical safety issues can be expected, and allows the development of strategies to mitigate these issues. Local regulatory guidance will be necessary to determine the minimal or optimal monitoring time before moving on to these more advanced studies, and this decision may be determined by the disease, the age of the patient(s), and the specific product used.

4.1 Characteristics of the Cell Product and its Manufacturing Process

Many characteristics of a cell therapy product can influence the nature and duration of clinical follow-up. The source of the cell therapy product, whether allogeneic or autologous, can pose certain challenges in determining patient follow-up. For example, allogeneic cells have a greater risk of causing immunogenicity than autologous cells. This may, for example, require monitoring for Graft versus Host Disease in the recipients. However, depending on the site and route of administration, allogeneic cells may be cleared from the recipient more rapidly than autologous cells. Thus, autologous cells, particularly manipulated autologous cells, may have greater potential for long-term persistence and long-term risks to the recipient. In addition, autologous products may be more difficult than allogeneic products to trace in the patient or study subject. This difficulty in tracing the product may make it more difficult to assign attribution of adverse events, such as the etiology of a tumor.

The type of cell and differentiation state of a therapeutic cell can also have an impact on the nature and duration of clinical follow-up. For example, well-differentiated cell types such as cartilage or lymphocytes may be less tumorigenic and therefore require less rigorous and shorter duration of follow-up when compared to undifferentiated mesenchymal stromal cells or undifferentiated embryonic-derived cells. Since the differentiation process of such embryonic-derived cells may be may be halted at different stages (stem to progenitor to fully differentiated cells), the fact that the progenitor stage holds a greater differentiation potential as compared to its fully differentiated counterparts must be considered. The issue of potential de-differentiation (i.e., reverting back to a less-differentiated stage), which could also increase the risk of tumorigenicity, has to be considered as well.

Manufacturing steps, such as long-term culture, may alter the cellular characteristics in ways that increase the risks of the product. One example would be the occurrence of chromosomal aberrations/instability. In some cases, the more the cells are manipulated, the greater are the unknowns about the risk of an adverse event. In addition, residuals from the manufacturing process and animal-derived ingredients could increase immunogenicity or the risk of infectious disease transmission, and thereby influence the product's safety.

Similarly, cell adhesion may promote cell survival, growth, and differentiation. Therefore, for cellular products that include a scaffold or other structural component, survival of the cells may be longer-term, with associated long-term risks. In such cases, biomaterial compatibility and interactions between the matrix or scaffold and the cell product also need to be considered.

4.2 Characteristics of the Study Population

In general, study population characteristics (e.g., type and severity of disease, clinical indication, age, gender, and immune competency) should be considered. Pediatric subjects might require longer and more detailed monitoring (e.g., monitoring of growth and development). While there may be as yet undocumented safety issues, where suitable medical input should be sought, risks such as immunogenicity and tumorigenicity are generally relevant in all populations. Cell therapy recipients who are not immune competent might be at higher risk for tumor formation. In addition, the cellular product might persist longer in recipients who are not immune competent than in recipients who are immune competent, thus placing these immune-incompetent recipients at risk for a longer duration. However, depending on the intended indication, long-term persistence of the cellular product may be desirable for optimal efficacy.

4.3 Posology

Posology considerations include the site and route of administration (e.g., subcutaneous vs. intravenous, or directly into an organ), speed of administration, number of administrations, and dose. Cell administration into vital internal organs (e.g., the brain, spinal cord, eye, or heart) would generally require more intensive (e.g., more frequent) and longer duration of follow-up than administration of cells into less critical organs or tissues (e.g., skin, fat, skeletal muscle), although local problems and tumorigenicity might be an issue in all cases. The level of concern attached to any specific site (or route) of administration will be informed by any available nonclinical or clinical data on cellular survival, proliferation, differentiation, and migration associated with that specific route of administration, as well as by the intended indication and type of product.

Faster speed of administration, intravenous or intracardiac route of administration, and/or higher cell number and cell size may require special immediate and short-term monitoring, as there may be an increased risk of emboli formation and damage to vessels in the lungs and other critical organs. Such risks should be evaluated and taken into consideration when planning clinical follow-up.

As for most therapeutic products, there might be a direct relationship between dose and long-term safety for cell therapy products. However, for most cell therapy products, there are not sufficient data to characterize the exact relationship between specific dose levels and long-term safety. In the absence of such data, it may be prudent to opt for longer-term monitoring.

4.4 Procedures or Concomitant Therapies

Procedures or concomitant therapies are often needed to administer a cell therapy product. Examples include bone marrow aspiration, immunosuppressive therapy, chemotherapy, and the use of special procedures to deliver the cell therapy product to the target location. These procedures and concomitant therapies may affect the short- and long-term safety of the cell therapy treatment. Therefore, their effects, adverse events, and interactions, if any, should also be monitored.

4.5 Previous Experience and Existing Knowledge

Previous clinical experience (e.g., published experience) with the product or with similar products (e.g., cells of the same origin, manufacturing process, route of administration, indication) can be taken into account, although the comparability of the products is often difficult to ascertain. This difficulty is increased by the fact that publications often do not reveal the manufacturing process in sufficient detail.

Safety results from previously conducted clinical trials and applicable data from in vivo and in vitro preclinical studies should also be considered as part of the weight-of-evidence when evaluating an investigational cellular product. Animal studies can be particularly informative with regard to cell fate post-administration, including cell survival/engraftment, distribution, persistence, differentiation, and tumorigenic potential. Data from preclinical studies can help guide elements of the clinical trial design, particularly the dose-escalation scheme, dosing regimen, and monitoring plan. However, animal data generally does not provide relevant information regarding the risk of immunogenicity in humans.

In conclusion, any previous non-clinical or clinical experience with the product, and with similar products, would be relevant to the design of the long-term follow-up. Considerations and elements of the long-term follow-up should be used to support the design and implementation of the risk management planning and risk minimization activities usually required for cell therapy product marketing authorization (e.g., Risk Mitigation Program (RMP), Risk Evaluation and Mitigation Strategies (REMS)).

5. CONCLUSION

Due to their unique pharmacokinetic/pharmacodynamic properties, cellular therapy products can have substantial and yet unknown risks for recipients. The nature and duration of follow-up necessary for patients receiving cell therapy products will vary, depending on the combined assessment of many different factors. Regulatory bodies and sponsors should consider the risk-related principles discussed above in determining the appropriate nature and duration of follow-up for each recipient of a cellular therapy, taking into account post-marketing commitments for each

Disclaimer

This document reflects the views of subject matter experts participating in the IPRP Cell Therapy Working Groups (CTWG) and should not be construed to represent the official views of any given regulatory authority participating in the IPRP.