A Cell Graft or a Drug? Legal and Practical Aspects of Somatic Cells Application in Graft-Versus-Host Disease Experimental Treatment: The Polish Experience

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ABSTRACT

Introduction. Allogeneic hematopoietic stem and progenitor cell (HSPC) transplantation and organ transplantation are well-established treatments for different conditions. Graft versus host disease (GvHD) is a major complication in both methods. There has been a rapid increase in the application of nonhematopoietic somatic cells, such as mesenchymal stem cells and regulatory T cells in GvHD experimental therapy. According to current European Union (EU) law, human cells intended for human application can be considered either as cell grafts or as advanced therapy medicinal products (ATMPs).

Objective, Materials and Methods. The aim of the paper is an attempt to answer, based on GvHD experimental treatment data as well as existing EU and Polish law, whether cells cease to be cells (cell grafts) and becomes drugs (ATMPs); if yes, when; and what are the consequences of such situation both for patients as well as for physicians engaged in the treatment process in Poland.

Results and Discussion. Data analysis confirmed the interest in the experimental GvHD cell therapy. In the vast majority of analyzed cases the in vitro culture step in the cell preparation protocols has been foreseen. Therefore, the answer to title question was unambiguous—expanded cells are recognized in EU as ATMPs. In borderline cases, a scientific recommendation by the Committee for Advanced Therapies (CAT) of the European Medicines Agency (EMA) can play an important auxiliary role; however, it is currently neither required by Polish law nor legally binding in Poland.

SEVERE graft-versus-host disease (GvHD) is a life-threatening inflammatory complication that can be observed after allogeneic hematopoietic stem and progenitor cell (HSPC) transplantation, as well as, albeit less frequently, after solid organ transplantation. It results from immune-mediated attack of recipient tissues by donor T cells and is associated with significant morbidity and mortality [1–3]. Standard treatment for severe GvHD is with high-dose corticosteroids, which induces a durable complete response in approximately 30% to 40% of patients. However, the prognosis for steroid-refractory acute GvHD remains poor, with an approximate 20% long-term survival rate; in cases of steroid-refractory chronic GvHD, long-term survival is diminished and disabling morbidity is common [4]. Therefore, both acute and chronic steroid-refractory GvHD are of growing interest for experimental cell therapies, in which 2 main types of cells are applied, namely mesenchymal stem/stromal cells (MSCs) and regulatory T cells (Tregs).

Mesenchymal Stem/Stromal Cells

MSCs are defined as self-renewing, multipotent progenitor cells with multilineage potential. In 2006, the minimal criteria for definition of MSCs were published by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy [5]. MSCs have been shown to possess an enormous number of

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immunomodulatory properties in vitro and in vivo, regulating both adaptive and innate immune responses [3]. Therefore, in the last decade a large number of clinical studies were conducted worldwide by the administration of MSCs from different sources and expanded in vitro by several alternative methods in patients suffering from severe steroid-resistant GvHD after HSPC transplantation, as well as a GvHD prophylaxis [1,3]. In 2012, a vast systematic review and meta-analysis was published to comprehensively summarize the safety of systemic MSC administration in different conditions, such as ischemic stroke, Crohn's disease, cardiomyopathy, myocardial infarction, as well as GvHD during clinical trials performed in the years 1950 to 2011. In the group of 36 studies that met inclusion criteria, only 8 were randomized controlled trials [6]. It was emphasized that clinical trial data are incomplete and there are significant discrepancies between results. It also was noted that the efficacy of MSCs as a preventive measure during HSPCT and in patients with chronic GvHD was less clear then the efficacy of MSCs in patients with acute GvHD. In order to improve the therapeutic effectiveness of MSCs, there is an urgent need to standardize MSC isolation and in vitro expansion protocols as well as their dosage, time, and route of administration [3].

Regulatory T Cells

$CD4^+$, $CD25^+$, and $Foxp3^+$Tregs play a crucial role in suppressing exuberant immune system activation and promoting peripheral immunologic tolerance [7]. These characteristics, as well as observations that the low number of Tregs in the peripheral blood after HSPC transplantation can be associated with the risk of GvHD [8,9], were one of the main reasons to initiate small-scale clinical studies concerning the application of Tregs from different sources and expanded in vitro to save patients with severe GvHD [10,11] or to prevent GvHD onset in patients after HPSC transplantation [12–14]. Emerging data support the safety and efficacy of Treg immunotherapy protocols; however, similar to the clinical application of MSCs, investigators will need to overcome significant hurdles, including Treg stability, isolation, and storage of Treg subpopulations, and off-target effects of in vivo Treg strategies [7,15].

European Union Tissue and Cell Directives

In the last decade, along with the increase in gathered evidence, new challenges arose for European scientists, clinicians, and patients—namely, new regulations. Tissue procurement, tissue banking (in its broadest sense, i.e. including tissue processing, testing, preservation, storage, and distribution), as well as tissue transplantation have a long history. The first scientifically documented descriptions of tissue transplantation date back to the beginnings of the 20th century or even the 19^{th} century. The history of cell procurement, banking, and transplantation is shorter. However, until the mid-2000s, donation, procurement, testing, processing, storage, and distribution of human tissues and cells for application in human beings were essentially unregulated at the level of the EU and these issues were regulated differently in each EU Member State.

In 2002, the proposal for the new European rule was presented by the European Economic and Social Committee [16]. In late March 2004, only one month before Poland, along with nine other European countries became full members of the EU, the first of the so-called European Union Tissue and Cell Directives (EUTCDs) – directive 2004/23/EC - was published [17]. Two years later, two implementing measures, also known as technical EUCTD –Directive 2006/17/EC and Directive 2006/86/EC, were issued [18,19]. The deadlines for transposition into national law in each EU Member State of the "mother" Directive 2004/23/EC, the "first technical" Directive 2006/17/EC, and the "second technical" Directive 2006/86/EC, were as follows: April 7, 2006; November 1, 2006; and September 1, 2007, respectively.

Transposition and Implementation of EUTCDs in Poland

In Poland, the first EUTCD in the field of somatic tissues and cells was enacted under the "Cell, Tissue and Organ Recovery, Storage and Transplantation Act" of July 1, 2005 (hereinafter the Polish Transplantation Act) which entered into force on January 1, 2006 [20]. Both technical directive, i.e. Directive 2006/17/EC and Directive 2006/86/EC, in the field of somatic tissues and cells, were transposed by the numbers of implementing acts (orders) issued under the Polish Transplantation Act.

From a historical point of view, it is worthwhile to remember that the first dedicated Transplantation Act was announced in Poland in 1995 and came into force in 1996. However, human connective tissue grafts such as bone, cartilage, tendon, pericardium, skin, and amnion membrane grafts began to be prepared at the Central Tissue Bank in Warsaw, Poland as of 1963. Shortly afterwards, due to the great interest of physicians and huge clinical demand, tissue banks were created in Poland to prepare, preserve, store and distribute all kinds of tissue grafts, including heart valve grafts and corneal grafts. It must be emphasized that from the very beginning, even in times when the Iron Curtain divided the continent of Europe, the activities of most tissue banks in Poland were not only limited to the preparation of tissue grafts. In these banks, in collaboration with scientists and doctors from Polish medical universities, human somatic cells grafts such as grafts of keratinocytes, chondrocytes, and osteoblasts were prepared. It is worth noting that although cell grafts have been used in humans, the high cost of the procedure, which greatly limited the scale of such projects, could often be covered only with funds for basic (not applied) research. Regarding HSPC procurement (collection), processing (preparation) and transplantation in Poland, the first successful transplantation of HSPC procured from bone marrow of a related donor was carried out in 1984, transplantation of autologous bone marrow HSPC