The European Court of Human Rights' Ruling on Unproven Stem Cell Therapies: A Missed Opportunity?

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ABSTRACT

On May 6th 2014, the European Court of Human Rights added yet a new element to the judicial history of stem cells as it ruled in *Durisotto v. Italy* [appeal n. 62804/13]. The ruling rejected a patient claim to access an unproven cell therapy—an outcome that is certainly to be welcomed. However, this ruling is a missed occasion to clarify and reaffirm some important legal distinctions that could have greatly benefited the whole field of regenerative medicine. We claim that the ethical and political assumptions that sustain the regulation of expanded access programs to new therapies should be carefully scrutinized, with particular attention to the justifications for the risks connected to unconventional therapies. A clear legal definition of what counts as compassionate cure as distinct from unregulated and untested therapies cannot be provided unless those points are previously addressed.

> The court has implicitly, and unintentionally, endorsed the possibility that unproven therapies could be legitimately considered as compassionate treatments.

INTRODUCTION

It is not rare for stem cells to become matters of public controversy, political debate, and judicial decisions. As a matter of fact, stem cells have so far had a rather turbulent public life. Highly controversial matters relative to the public funding, derivation, use, and intellectual property protection of stem cells have been discussed and adjudicated by parliaments, governments, and courts around the globe [1–3]. Two famous cases recently made headlines. In late 2011, the European Court of Justice decision in *Brüstle v. Greenpeace* (Case C-34/10) revoked a German patent on a cell line because its derivation entailed the destruction of a human embryo [4]. The other famous decision dates back to August 2012 when, in *Sherley v. Sebelius*, the U.S. Court of Appeals in Washington, DC, confirmed the legitimacy of federal funding on human embryonic stem cell research. In January 2013, the U.S. Supreme Court further reaffirmed this point, refusing to hear an appeal of the plaintiff [5].

On May 6, 2014, the European Court of Human Rights (ECHR) added yet a new element in the judicial history of stem cells as it ruled in *Durisotto v. Italy* [101]. Contrary to other landmark rulings, the object of the decision was not the legitimacy of deriving cells from human embryos for research purposes. This time, the controversy was relative to the rights of patients who, in the absence of any other therapeutic possibility, decide to resort to unproven treatments—in this case, stem cell therapies.

In *Durisotto v. Italy*, for the first time, a European Court had to establish whether access to a stem cell treatment can be granted according to the principles of the European Convention of Human Rights. This ruling is of interest for a number of reasons. For starters, it signals that stem cells, and the controversies surrounding them, may be moving closer to the clinical and therapeutic side of the field—a fact that should be carefully monitored by scholars interested in the governance of regenerative medicine [6]. Second, the case reminds us that the current regulatory framework for the development and provision of cellular therapies is far from stabilized and may

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indeed undergo serious challenges [7]. Finally, but equally important, the case testifies of the hype surrounding cell therapies and will thus have repercussions on how we think about patients' entitlements vis-à-vis new therapeutic approaches in this field.

The decision of the court in *Durisotto v. Italy* rejected a patient's claim to access an unproven cell therapy—an outcome that is certainly to be welcomed. However, this ruling is a missed occasion to clarify and reaffirm some important legal distinctions that could have greatly benefited the whole field of regenerative medicine by reducing the likelihood of similar cases arising in the future and being ruled in a different way.

The European Court of Human Rights

In order to illustrate the case and to discuss the ambiguities of the ruling, let us first recall the basic features of the ECHR. This court was established in 1959 to implement the *Convention on the Protection of Human Rights and Fundamental Freedoms*, signed in Rome in 1950 by the 47 member states of the Council of Europe. Since 1998, individuals have been having the possibility to appeal to the court directly if they think a member state has violated human rights or fundamental freedoms established by the convention. This is, for instance, what happened in the *Durisotto* case in September 2013.

The ECHR is the judicial organ of the Council of Europe.[1] It is thus in view of the protection of human rights that the Council of Europe and the ECHR historically became interested in matters of health care provision. The aim of the ECHR in this context is to ensure that states do not violate the provisions of the convention in matters of public health and in the delivery of health care.

EUROPEAN COURT OF HUMAN RIGHTS
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The European Court of Human Rights created a fact sheet of recent health-related decisions—including a section on access to experimental drugs or treatment. The fact sheet is available as a PDF at www.echr.coe.int/Documents/FS_Health_ENG.pdf

The case

Mr. Durisotto is an Italian citizen acting as the legal guardian of his daughter who, since adolescence, has been suffering from a degenerative cerebral disease (metachromatic leukodystrophy, MLD).

In Italy, starting in 2009, a private group called Stamina Foundation has been offering cell-based therapies to patients affected by a variety of serious neurodegenerative disorders (including MLD), under a compassionate use framework [8]. Stamina cell products (both autologous and allogeneic) consist of bone marrow aspirates claimed to contain mesenchymal stem cells. The latter are said to be treated to instruct neural fate differentiation before being infused into patients (generally intravenously) in cycles of five injections, but the protocol has never been disclosed by Stamina. At present, there exists no published evidence that the neural differentiation of mesenchymal cells is biologically possible, nor does any publication support the safety and efficacy of the Stamina treatment. All that supports the method is self-reports by treated patients who initially were charged thousands of euros for the treatment.

In late 2011, for reasons that are still the object of judicial investigation, the method was made available in a public hospital in the North of Italy. Given its scientific implausibility, this fact raised harsh reactions and the case later became a major public controversy in the country [9].

Italian law explicitly allows the compassionate use of gene and cell therapies in the absence of therapeutic alternatives and in cases of emergency provided that certain conditions are met: existence of scientific data to justify the use of the therapy, informed consent, and a positive opinion from an ethics committee (Decree, 2006) [10]. Stamina has always claimed to act under the legal framework of the 2006 decree, but an inspection by the Agenzia Italiana del Farmaco (AIFA the Italian FDA) revealed in 2012 that none of the above conditions were met. The activities of Stamina were thus halted, but this fact ignited rather vocal protests on the part of Stamina's patients and their families. As a result of the mounting turmoil, in March 2013, a new ministerial decree granted access to Stamina's procedure for those patients who had already started the treatment at the moment of the entry into force of the decree [11].

Back in April 2013, Mr. Durisotto had requested the therapy to be administered to his daughter as a compassionate stem cell therapy. An Italian court had initially approved his request. At a later stage, however, the court reverted its decision, noticing that the 2013 decree did not authorize those therapies for patients who had not already started the cycle of Stamina infusions.

To appellate against this decision to the ECHR, Mr. Durisotto applied to the European Court of Human Rights claiming the infringement of several articles of the European Convention of Human Rights: Article 2 (right to life), Article 8 (right to respect for private life) and Article 14 (prohibition of

[1]The Council of Europe is an intergovernmental organization—the oldest regional organization of the European continent (established in 1949). It is clearly distinct from the European Union, although all the members of the union belong to it. "The maintenance and further development of human rights and fundamental freedoms" feature in the very first article (art. 1.b) of the Statute of the Council of Europe. Furthermore, the condicio sine qua non for a state to belong to the Council of Europe is the respect of human rights (art. 3 of the statute).

discrimination). However, following its jurisprudence on access to compassionate treatments [12], the Court rejected Mr. Durisotto's claims as manifestly unfunded and therefore not admissible. In particular, the ECHR considered the provisions of the Italian ministerial decree of 2013 (as applied by the Italian court) proportionate and not discriminatory. Furthermore, the court noticed that, in decisions concerning access to compassionate therapies for patients affected by very severe pathologies, member states retain a large margin of autonomy, and that the international judge cannot substitute national authorities in determining the degree of acceptable risk for patients claiming access to compassionate treatments with experimental therapies.

Nonetheless, even if the arguments developed by the court are consistent with its previous decisions, European judges did not take this occasion to reaffirm the distinction between compassionate use and unproven therapies, and how this distinction bears the legal balancing of individual and collective interests.

Demarcating compassionate treatments from unproven therapies

The term "compassionate therapy" is clearly defined by the European Union legal framework in its Regulation (EC) no. 726/2004 of the European Parliament and of the Council Article 83.2 as "a medicinal product [...] available for compassionate reasons to a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorization [...] or must be undergoing clinical trials." Since the implementation of this provision is up to member states [13], there is a certain degree of heterogeneity among different European countries [12, paragraph 51] [14].

Moreover, it is not clear if European regulations on compassionate use of conventional drugs also apply to cell therapies or if the latter fall under the hospital exemption clause for regenerative medicine products.[2] This is a serious and worrisome ambiguity—one that could be exploited by commercial actors to bypass clinical trials and marketing authorization procedures for stem cell products.

At any rate, the cell product used by Stamina clearly fails to meet the necessary criteria of the European Regulation on compassionate treatments as Stamina has not applied for its marketing authorization, nor has it ever conducted a clinical trial to test its safety or efficacy. Stamina's protocol also falls short of the specific requirements set out by the Italian legislation for the compassionate use of cell therapies[3] [10]. In this respect, the fact that the court continued to refer to the provision of Stamina's treatment as compassionate therapy is actually misleading, as this treatment does not legally qualify as a compassionate treatment at all. Moreover, the court reaffirmed the legal validity of the 2013 decree as an objective reason to justify that Durisotto's daughter was denied the cure, whereas other patients in similar circumstances were authorized to receive it (for the reason that they had previously started the cycle of infusions). In confirming the proportionality and reasonability of the 2013 decree, the court implicitly endorses the possibility that totally unproven therapies that are neither undergoing marketing authorization nor were ever properly tested in a clinical trial could be legitimately considered as compassionate treatments and thus authorized for desperate patients. This is certainly not the intention of the ECHR, as the court recognized the lack of scientific validation of the Stamina method. Nonetheless, the decision contains such element of ambiguity that would have better been avoided or clarified.

Although the decision has resulted in a foreseeable (and desirable) outcome—confirming the validity of the Italian court ruling not to grant access to the treatment—it would have been more powerful in guiding judges for future similar cases, had it clearly distinguished compassionate treatments from unproven therapies.

Balancing the interests at stake

As the hype grows around regenerative medicine, patients' hope to attain benefits from anything that even remotely relates to stem cell therapy takes highly controversial directions. For sure, expanding access to therapies that are not yet fully validated can at times be in the best interest of patients with no other therapeutic options. This reasoning has been growing ever since the HIV/AIDS epidemic in the Eighties [15] and the rise of patient activism [16] that prompted the establishment of "expanded access" programs in the United States. However, we have to remain wary of stretching this concept beyond reasonableness. Therapeutic benefit from compassionate treatments (or expanded access, as it is called in the United States) is the exception, not the rule. Even more so, granting patients access to unproven therapies, other than being unlikely to provide any benefit, can actually result in serious harm. The fact that a patient has exhausted all other therapeutic options is not enough to overlook those considerations.

[2]The hospital exemption mentioned in the 1394/2007 regulation on advanced therapy medicinal products (art. 28) "allows for a medicinal product containing stem cells to be made available to an individual patient in a European hospital under the exclusive professional responsibility of a doctor. This is a custom-made product that is prepared on a non-routine basis according to specific quality standards. It is authorised for use by the regulatory authority of the Member State where the product is made." (European Medicinal Agency, public statement, Concerns over unregulated medicinal products containing stem cells, April 16, 2010).

[3]The hospital exemption clause has not yet been implemented in Italy; as a consequence, the preexisting national regulation is still valid.

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In this respect, we have to seriously scrutinize the ethical assumptions that sustain the regulation of expanded access programs. In particular, the justifications for the risks connected to unconventional therapies need to be carefully reevaluated. This is true of conventional forms of compassionate use of chemical drugs, and even more so of expanded access to biological drugs and regenerative medicine products.

A clear legal definition of what counts as compassionate treatment as distinct from unregulated and untested therapies cannot be provided unless those ethical points are previously addressed. In a compassionate use setting, the responsibility for the assessment of safety and efficacy pertains to dedicated regulatory agencies. However, in the Italian case, this important prerogative shifted from AIFA to the minister and then to judges, producing the controversy that we have described.

At a more general political level, *Durisotto v. Italy* reaffirms national states' jurisdiction over the provision of cell products in compassionate settings. However, a patchy regulatory environment can actually become extremely problematic for public health care systems in Europe. As it happened in Italy, as a consequence of the soaring number of requests for access to unconventional cell therapies, costs can explode and resources can unfairly be drawn from other, more ordinary but also more effective and needed health services. Those costs have been estimated to be of such magnitude as to drive public health care systems to bankruptcy, should unproven stem cell therapies be made freely available to patients [102].

A more rigorous regulation of compassionate stem cell therapies is therefore imperative if we want to attain a reasonable balance between individual expectations and public interest in the domain of biomedical innovation. Ethical, legal, and public health considerations must be carefully discussed in order to find acceptable solutions.

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REFERENCES

Primary Literature

1. Gottweis H, B Salter and C Waldby. (2009). *The Global Politics of Human Embryonic Stem Cell Science: Regenerative Medicine in Transition*. Palgrave Macmillan, Basingstoke, Hampshire, UK.
2. Jasanoff S. (2011). *Designs on Nature: Science and Democracy in Europe and the United States*. Princeton University Press, Princeton, NJ.
3. Jasanoff S. (2011). *Reframing Rights: Bioconstitutionalism in the Genetic Age*. MIT Press, New York.
4. Triller Vrtovec K and C Thomas Scott. (2011). The European Court of Justice ruling in *Brüstle v. Greenpeace*: the impacts on patenting of human induced pluripotent stem cells in Europe. Cell Stem Cell 9:502–503.
5. Wadman M. (2013). High court ensures continued US funding of human embryonic-stem-cell research. Nature. doi: 10.1038/nature.2013.12171.
6. Blasimme A. (2013). Translating stem cells to the clinic: scientific societies and the making of regenerative medecine. Quaderni n.2:29g st.
7. Meslin EM, A Blasimme and A Cambon-Thomsen. (2013). Mapping the translational science policy "valley of death." Clin Transl Med 2:14.
8. Blasimme A and E Rial-Sebbag. (2013). Regulation of cell-based therapies in Europe: current challenges and emerging issues. Stem Cells Dev 22 Suppl 1:14–19.
9. Abbott A. (2013). Stem-cell ruling riles researchers. Nature 495:418–419.
10. Decreto Ministeriale Dicembre 5, 2006, published in the Official Journal March 9, 2007. www.gazzettaufficiale.it /eli/id/2007/03/09/07A02073/sg
11. Decreto Legge n°24/2013, Marzo 25, 2013. www.gazzettaufficiale.it/eli /id/2013 /03/26/13G00064/sg
12. *Hristozov and others v. Bulgaria*, nos. 47039/11 and 358/12, 04/29/2013. http:// hudoc.echr.coe.int/sites/eng/pages/search .aspx?i=001-114492#{%22itemid%22: [%22001-114492%22]}
13. European Medicines Agency. Guideline on compassionate use of medicinal products (EMEA/27170/2006). www.ema.europa.eu/docs/en_GB/docume nt_library/regulatory_and_procedural_g uideline/2009/10/WC500004075.pdf
14. Whitfield K, et al. (2010). Compassionate use of interventions: results of a European Clinical Research Infrastructures Network (ECRIN) survey of ten European countries. Trials 11:104.
15. Epstein S. (1996). *Impure Science: AIDS, Activism, and the Politics of Knowledge*. University of California Press, Oakland, CA.
16. Dresser R. (2001). *When Science Offers Salvation: Patient Advocacy and Research Ethics*. Oxford University Press, New York.

Websites

101. *Durisotto v. Italy* n°62804/13 (2014). http://hudoc.echr.coe.int/sites/eng/pages/search.aspx?i=001-144670, decision only in French.; press release www.eucellex.eu/wp-content/uploads/2014/06/Decision-Durisotto-v.-Italy-refusal-to-authorise-access-to-experimental-treatment.pdf

102. De Luca M. (2013). Metodo Stamina, la cura che non c'è costerebbe decine di miliardi al Ssn. Il Sole 24ore, 10 August 2013. www.ilsole24ore.com/art/notizie/2013-08-10/metodo-stamina-cura-costerebbe-165704.shtml?uuid=Abh6u6LI