doi:10.1038/mt.2013.1

Molecular Therapy

"Special Exemptions": Should They Be Put on Trial?

A series of recent articles in *Molecular Therapy* has discussed the pros and cons and, more importantly, the ethics of using experimental therapies to treat patients outside the context of a formal clinical trial.[1–3] There has also been a divide between North America and Europe with respect to this discussion in that there is legislation that allows off-trial treatment in Europe but no such regulation in the United States. In Europe, experimental gene and cell therapies constitute one of three types of advanced-therapy medicinal products (ATMPs) that fall under EU medicines legislation, and their use in clinical trials requires a clinical trial authorization.

However, within medicines legislation there exist certain "exempt" manufacturing schemes for use of experimental therapeutics outside of formally authorized clinical trials that aim to meet the special clinical needs of individual patients. For example, the "hospital exemption" scheme allows the use of ATMPs that are "prepared on a non routine basis and used within the same Member State in a hospital in accordance with a medical prescription for an individual patient."[4] The exemption was provided "in recognition of the small scale and developmental nature of activity carried out in some hospitals, which argued for a degree of flexibility over the nature of regulatory requirements."[4] The "specials" scheme of the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom (http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedalicence/Medicinesthatdonotneedalicence/index.htm), under conditions similar to the above, allows the manufacture, import, and export (provided the receiving member state has the appropriate legislation for their import) of unlicensed products for use in patients under the prescription and direct responsibility of the patient's physician.

The uptake and implementation of both of these exemption schemes are under the jurisdiction of the regulatory authority of each EU member state. In the United Kingdom, the schemes are permitted only in institutions that have been granted the specific manufacturing license by the MHRA following a successful inspection, which ensures that all products generated for exemption use are generated under good manufacturing practice conditions. Simply put, this allows certain gene and cell therapies to be used to treat individual patients to meet their special clinical needs, outside the context of a clinical trial or when a clinical trial is not available. This does not require inclusion–exclusion criteria or a specific dosage schedule other than those "under the exclusive professional responsibility of a medical practitioner"; it requires only ethical approval according to local institutional governance requirements. Critics have argued that, because their use is not governed by the formal rigor of a clinical trial, this provides a carte blanche for physicians to treat patients with untested products that may be potentially harmful or have only limited success. On the contrary, a rigorous, formal site-inspection schedule ensures that the interests and safety of the patient are paramount.

As investigators working in the field of gene therapy for rare diseases and having used the "specials" license to treat specific patients, we argue that the judicious use of this scheme has been invaluable in elucidating specific disease- or treatment-related issues, which would have been nearly impossible within the context of a formal study. Importantly, it has also allowed patients with limited treatment options access to potentially beneficial therapies when no trial has been available. As a result, the information gained has facilitated the design of future clinical studies and expedited their implementation. While we recognize the concerns expressed by critics, there are a number of safeguards in place. Although patients are treated outside of a trial and without formal ethical approval by an institutional review board, we adhere to a local ethical framework that has been proposed by a clinical ethics committee at our institution and is designed to protect patient interests.[5] Patients are treated according to the criteria that are to be proposed for a future study or when standard treatment options are not available or are deemed potentially too harmful because of the patient's clinical state. We also ensure that in these cases there is discussion and agreement among a multidisciplinary team that this is the most appropriate course of action. Patients are fully informed that treatment is outside of a trial context, and we

ensure that appropriate information is made available to the patient and a personalized consent form is signed. We inform national regulators (the MHRA and the national ethics committees) of the patient details and proposed treatment, although we do not necessarily need—and they cannot give—formal approval. Regulators are also informed of patient progress and outcome.

The need to use either of these exemptions is more acute in rare or very rare (incidence of <1:100,000) disease cohorts. In such conditions, the standard paradigm of progression through phase I, II, and III studies before taking a therapy to market authorization is simply not feasible. In the majority of cases, initial studies are phase I/II and designed to test both efficacy and safety; most therapies never reach phase III because of the sheer lack of patient numbers and treatment options available. Clinical trials in gene therapy for immunodeficiencies have recruited 10–20 patients to prove efficacy and determine safety.[6–8] Legislation designed for standard therapeutic agents for which hundreds or thousands of study patients are recruited and amendments can be tested in future large cohorts is simply not applicable to cohorts of patients with rare diseases, for whom such large numbers are not possible. Despite the extensive preclinical development undertaken before initiation of a clinical trial, it is clear that information on efficacy and toxicology obtained in animal models is not always predictive of the human response.[9] It is also the case that when conducting trials with such small numbers of patients, the "every patient counts" mantra is never more applicable. Therefore, there is a greater need to ensure that the trial design and practicalities are correct before trial initiation; otherwise, as we have found, we generate a list of substantial amendments that far exceeds the number of patients enrolled.

For these reasons, we have used the exemptions to treat small numbers of patients (one or two) before initiating a formal clinical study. In a recent example, a patient with adenosine deaminase (ADA) deficiency was treated with a novel lentiviral vector before trial initiation. The subject was in clinical need of treatment, had a very poor response to enzyme replacement, and had no suitable donor options for transplant. To obtain a maximal number of $CD34^+$ stem cells, which is known to be a critical determinant of successful outcome, we considered using mobilizing peripheral blood. There is little experience on mobilization in ADA deficiency, and the only report (in two patients) dates back to 1996 (ref. 10), before the use of plerixafor. The draft trial protocol had therefore excluded the use of mobilized peripheral blood stem cells. In this individual, granulocyte colony-stimulating factor and plerixafor-mobilized cells yielded more than 10^6 $CD34^+$ cells/kg, which is considerably higher than the marrow $CD34^+$ cell dose we had obtained from eight previous ADA-deficient patients. On the basis of this experience, we were able to configure a trial protocol to include mobilized peripheral blood stem cells as the source of $CD34^+$ cells. In another case, for a different immunodeficiency, we used the exemption scheme to treat a patient with an entirely new vector and thus for the first time demonstrated its biological activity in humans. The results have informed an imminent multicenter international clinical trial.

Highly productive discussions with regulators in the United Kingdom have led to an agreement that the use of an ATMP manufactured under an exemption is justified as long it is used where there is a clear clinical need and in limited numbers. We agree that treatment of a large series of patients in this way would be an abuse of this clause and not good practice. Carefully designed clinical trials remain the route by which to advance scientific knowledge and drive effective commercialization. However, the judicious use of an exemption scheme applied where there are limited conventional treatment options is very much in the interests of patients, academia, and larger pharma.

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