

The role of the Istituto Superiore di Sanità as the competent authority for Phase I trials in the translation of advanced therapies

Patrizia Popoli, Maria Francesca Cometa, Fulvia Fabi and Annarita Meneguz
*Secretariat of the Committee for the Evaluation of Phase I Clinical Trials,
Dipartimento del Farmaco, Istituto Superiore di Sanità, Rome, Italy*

Summary. Advanced therapy medicinal products (ATMP) can offer new, effective therapeutic options for the treatment of severe illnesses, including cancer, neurodegenerative and cardiovascular diseases. Translation of advanced therapies to the clinic has been slow despite significant academic research from academia and foundations. The implementation of 2001/20 Directive in Italy established that the development of an ATMP should follow the GXP rules – good manufacturing practice (GMP) for production, good laboratory practice (GLP) for non clinical safety studies and good clinical practice (GCP) for clinical trials. The high costs of GCP application and the needs for GMP facilities are perceived as the most important bottlenecks for the development of ATMP. Here it is pointed out that a strategic cooperation between different actors (academia, industry and experts in regulatory issues) is strongly needed. In particular, it is highlighted that the Istituto Superiore di Sanità, as the competent authority for the authorization of Phase I clinical trials, has a specific responsibility in fostering the translation of safe and effective therapies for human diseases.

Key words: translational research, early phase clinical trials, advanced therapy medicinal products.

Riassunto (*Il ruolo dell'Istituto Superiore di Sanità, come autorità competente per le sperimentazioni cliniche di fase 1, nella traslazione di terapie avanzate*). I prodotti medicinali per terapie avanzate (*advanced therapy medicinal products, ATMP*) possono rappresentare nuove ed efficaci opzioni terapeutiche per il trattamento di patologie severe come il cancro, i disturbi neurodegenerativi e cardiovascolari. Nonostante il grosso impegno profuso nella ricerca di ATMP da parte di università e fondazioni scientifiche, la traslazione delle terapie avanzate alla clinica è ancora piuttosto lenta. Con il recepimento in Italia della Direttiva 2001/20 si è stabilito che lo sviluppo di un ATMP deve seguire le regole delle GxP – buona pratica di fabbricazione (*good manufacturing practice, GMP*), buona pratica di laboratorio (*good laboratory practice, GLP*), buona pratica clinica (*good clinical practice, GCP*). L'elevato costo derivato dall'applicazione delle GCP e la necessità che la produzione avvenga presso stabilimenti autorizzati GMP, costituiscono il più importante collo di bottiglia per lo sviluppo di ATMP. In questo articolo viene messa in evidenza la necessità di una collaborazione strategica fra differenti attori quali l'accademia, l'industria ed esperti in problemi regolatori. In particolare è evidenziato il ruolo dell'Istituto Superiore di Sanità, in qualità di autorità competente per l'autorizzazione di sperimentazioni cliniche di fase 1, nel promuovere la traslazione di terapie con ATMP sicure ed efficaci.

Parole chiave: ricerca traslazionale, sperimentazioni cliniche di fase precoce, prodotti medicinali per terapie avanzate.

INTRODUCTION

The development of advanced therapy medicinal products (ATMP) may open novel avenues for therapeutic approaches in numerous diseases. It is felt that the new discoveries generally fail to be efficiently translated into clinical research and ultimately into clinical practice [1-4]. Such difficulties may be even more relevant for ATMP, since most of their development is still in the non-profit or in academic laboratories, and given the complexity of the

regulatory framework, the high costs and the needs for good manufacturing practice (GMP) facilities. Indeed, the Directive 2001/20 made good manufacturing, laboratory and clinical practice mandatory for all clinical drug trials, including academic trials, and not just commercial trials as previously. The good standard practice includes a large amount of paperwork, with documentation, monitoring, and audits, thereby increasing demands on resources. If the researchers have the possibility of obtain-

ing help from competent authorities (CA) in solving good standard practice problems, the obligations of the researchers might become practicable.

Strong initiatives and coordinated efforts are thus needed to support development and translation of new therapies.

Contributing to such a process will allow regulatory bodies to promote public health and to favor the translation of new treatments to the patients who need them.

THE ROLE OF THE ISTITUTO SUPERIORE DI SANITÀ IN EARLY PHASE TRIALS

Despite the registration process of ATMP for which the only regulatory subject involved is the European Medicines Agency (EMA), the clinical trial application (CTA) remains a national competent authority responsibility. However, the Clinical Trials Directives 2001/20/EC [5] was trying to harmonise the rules and administrative provisions governing clinical trials in EU by establishing a common procedure and creating the conditions that will help the regulatory authorities to coordinate such trials.

In Italy, the National Institute of Health (Istituto Superiore di Sanità, ISS) is the CA for the authorization of Phase I clinical trials, including those employing ATMP [6]. The CA for ATMP Phase II and III trials is the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA).

The authorization of a Phase I study represents the transition from the preclinical to the clinical phases, and it is thus a pivotal step in translational medicine.

Transition from non-clinical to clinical testing requires special precautions to minimize risks, and this may be particularly true for advanced thera-

pies. Indeed, the risks associated with novel technologies induces the implementation of stringent safety provisions.

Consequently, before progressing into first-in-man (FIM) trials both quality aspects (potency, identity, purity, sterility, viability) and non clinical aspects (immunogenicity, biodistribution, appropriate animal model, tumorigenicity) have to be carefully evaluated for the selection of the safe dose and the prediction of human response. The validity of conventional models to predict the safety and the efficacy of advanced therapies is generally poor.

In Italy, *ad hoc* guidelines were available for Phase I clinical trials and ATMP but they are now substituted by the EMA guidelines, available at European Medicines Agency site (www.ema.europa.eu).

The EMA guidelines regulate the ATMP area on different aspects of the requirements in terms of quality, safety and efficacy at both preclinical and clinical levels, of environmental risk assessment, of development and manufacture of lentiviral vectors and of follow-up of patients.

The Italian CA acts as a committee for Phase I clinical trials, and is supported by experts/assessors coordinated by the scientific secretary of committee and the administrative office.

THE ITALIAN CA PROCEDURES FOR ATMP

Currently there are no standard operating procedures (SOPs) *ad hoc* for ATMP. However, since 2004 [6, 7], the assessment is based on the following documents:

- the CTA;
- the investigational medicinal products dossier (IMPD) containing the quality, non clinical and

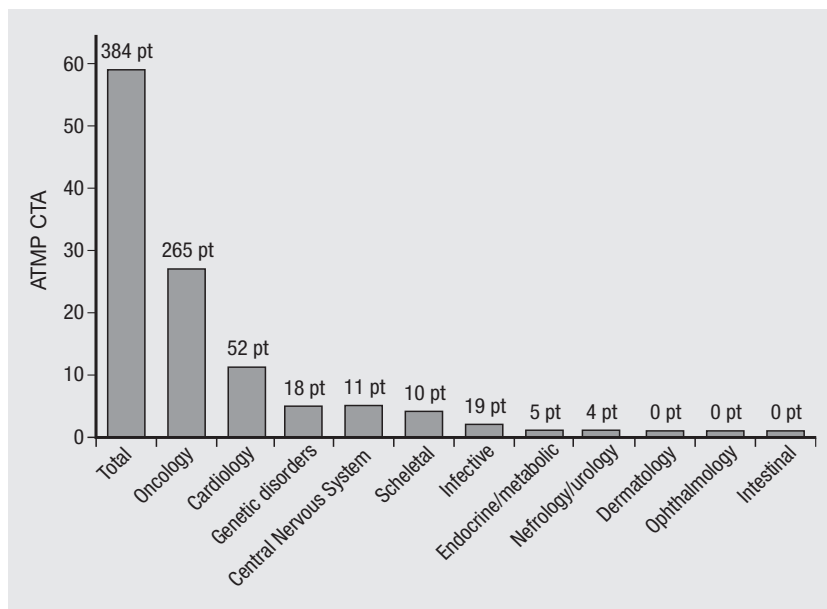


Fig. 1 | Clinical trial applications by therapeutic areas and treated patients (pt). ATMP: advanced therapy medicinal products; CTA: clinical trial application.

- clinical data sections (with the indication of version and data);
- the investigator's brochure (IB) (with the indication of version and data).

The ISS releases (or denies) the authorisation in the frame of a formal assessment report.

The overall schedule is defined by the Directive 2001/20 [6] and by the National Decree 439 [8]. Since 1997, 59 applications (15% out of total) around cell and gene therapy were filed, 50 authorised, with 2 currently under evaluation (*Figure 1*).

Most submissions are supported by non-profit organizations (83%), and are mainly proposed by single investigators developing the product in house on the basis of literature data. In most cases they are monocentric trials focused on secondary endpoints and enrolling limited number of patients.

The success of a multi-center trial for treating children with SCID (severe combined immune deficiency or "bubble boy disease") held from 2000 and 2002 was questioned when two of the ten children treated at the trial's Paris center developed a leukemia-like condition.

Clinical trials were halted temporarily in 2002, but resumed after regulatory review of the protocol in the United States, the United Kingdom, France, Italy and Germany. Following the French SCID experience, an additional National Decree was released in 2004 [9], with the specific aim to set up a database of patients treated with gene and somatic cellular therapy. The main goal was to register all patients involved in advanced therapy trials and to follow them in order to detect early signals of delayed adverse reactions. The database was established at the ISS.

POSSIBLE ROLE OF THE ISS IN SUPPORTING THE DEVELOPMENT AND TRANSLATION OF ATMP

The main mission of ISS in the field of drugs (and, in general, of medicinal products) is to guarantee the safety and the efficacy of drugs in order to protect public health.

At the same time, however, as the National Institute of Health, we have the specific duty to promote public health and to favor the translation of new treatments to the patients who need them.

It is recognized that ATMP represent a research area with a great potential impact for patients.

Despite the efforts aimed at the harmonisation of such a complex area, there are still many critical issues concerning the applications, which include:

- a lack of understanding of the importance of GXP for the management of clinical trial;
- a definition of investigational medicinal product;
- issues with production according to GMP;
- a lack of justification for the conduction of non clinical safety study;
- a lack of a proof of principle;

- inappropriate reference to other "similar" product;
- GLP batches different from GMP batches;
- no rationale for the choice of the first human dose in FIM trial.

For the above mentioned issues, in the last few years, there has been a decrease in the number of clinical studies involving ATMP in Italy.

Recognizing the need of a help-desk service on regulatory issues, the ISS has implemented a program of scientific advice.

The service (which is rapid, informal and free of charge) consists in the scientific discussion with ISS experts in order to provide advice and support for the preparation of the dossier for Phase I application. According to our current experience, as well as of the feedbacks we received so far, such an activity is considered very useful.

To further improve the program, technical internal meetings and continuous formation of ISS assessors are being implemented. Furthermore, dedicated personnel is involved in the coordination and planning of this activity.

For further information on the activity of the "Phase I secretary", please visit the website (www.iss.it/scf1).

CONCLUSION

ATMP show a great potential impact on public health, but translation to the clinic has been slow despite significant academic research. Although the good practice quality standard is often perceived as a mere bureaucratic obligation, implementation of quality assurance and quality control systems as requested from the Directive may well lead to better research and more valid conclusions.

In order to help their translation, a strategic cooperation involving all the interested actors is needed.

As a regulatory body, the ISS is contributing to this process by providing scientific advice on the preparation and presentation of the dossier for Phase I application.

Furthermore, experts from the ISS contribute to the technical-scientific debate on ATMP both at national and international levels.

Such an effort is an integral part of our mission which, in a comprehensive view, is that to favor the delivery of safe and efficacious new treatments to the patients who need them.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct of the activities reported in this paper.

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