Clinical Trials of Orphan Drugs in Latvia

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Introduction. Rare diseases (RDs) are life-threatening or chronically debilitating diseases with a low prevalence and a high level of complexity. Most of them are genetic diseases, the others being rare cancers, autoimmune diseases, congenital malformations, toxic and infectious diseases among other categories. The prevalence for a RD is currently defined as affecting no more than 5 per 10,000 persons in the EU. There are between 5,000 and 8,000 distinct RDs that affect between 6% and 8% of the total EU population.

Medicinal products intended for diagnosis, prevention or treatment of RDs are called orphan drugs (ODs). While evidence from randomized controlled trials (RCTs) with clinically relevant endpoints is the standard for granting marketing authorization, a host of challenges complicates the development of safe and effective ODs. These challenges include difficulties in attracting public and private funding for research and development, recruiting sufficient numbers of research participants for clinical trials (CTs), appropriately using CT designs for small populations (including lack of validated biomarkers and appropriate surrogate endpoints).

The aim. This study aims to evaluate the quality of CTs for ODs and RDs conducted in Latvia.

Methods. EU CTs register (https://www.clinicaltrialsregister.eu/) which provides public access to information extracted from the EU CTs database EudraCT was used. Data on 40 CTs of drugs for RDs (including 24 drugs with orphan designation) conducted in Latvia since 2004 till the end of 2012 were obtained to evaluate the following characteristics of CTs: RDs and ODs being studied, design of the CTs, primary endpoints, control, randomization, blinding, duration of the CTs and number of patients involved.

Results. The most studied disease was multidrug-resistant tuberculosis (MDR-TB) with 7 CTs conducted, followed by 3 CTs for pseudomonas aeruginosa infection in cystic fibrosis patients and acromegaly. There were 4 CTs conducted for Delamanid (OPC-67683), 3 CTs for Bedaquiline (TMC207), Tobramycin and Dopastatin (BIM-23A760). While 13 CTs (32.5%) were conducted in oncology field, 11 CTs (27.5%) in infectious diseases and 7 CTs (17.5%) in endocrine and metabolic diseases. Surrogate endpoints were used in 19 CTs (47.5%), clinical endpoints in 8 CTs (20%) and composite endpoints in 12 CTs (30%). Surrogate endpoints examples included sputum culture conversion used in 5 MDR-TB CTs, progression-free survival (PFS) used in 5 oncological CTs, insulin-like growth factor-1 (IGF-1) and growth hormone levels used in 3 acromegaly CTs. Overall survival was used only in 1 CT and 1 CT used quality of life as primary endpoint. Composite endpoints often included adverse events, evaluation of symptoms, physical examination, vital signs and laboratory assessment. 21 CTs (52.5%) were phase III and 13 CTs (32.5%) were phase II CTs. 24 CTs (60%) were RCTs from which 16 (40%) were double blind CTs. Placebo was used in 16 CTs (40%) and 9 CTs (22.5%) used active comparators. All studies except one were conducted in multiple EU member states and 37 CTs (92.5%) were conducted both within and outside the EU. Average duration of CTs was 32.2 months. 9 CTs (22.5%) involved subjects under 18. CTs included an average of 18 patients in Latvia, while the average number of patients included in CTs in the EU was 177 and 323 in the entire CT.

Conclusion. Mainly phase III CTs were conducted with the majority of CTs conducted in oncology field followed by infectious diseases (mostly MDR-TB). In almost a half of CTs surrogate endpoints were used. However, quality of CTs seems to be high since the majority of CTs conducted are RCTs and double blind method was often used. International collaboration and conduction of multicenter, multinational CTs is crucial in the field of RDs as recruiting a sufficient number of patients especially in small countries like Latvia would be impossible.