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Universal information structure as a tool of long-term follow-up monitoring in allergology

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The article is dedicated to the issues of organization of long-term follow-up monitoring of the patient population in real clinical practice. Every medical intervention is analyzed from the position of positive evidence of its effectiveness, safety and clinical-economic benefits. Although randomized clinical trials (RCTs) are the gold standard of evidence-based medicine, they feature a range of drawbacks; in some cases, such trials are infeasible or extremely complicated to perform due to certain aspects. Along with that, results of RCTs may not completely correlate with clinical practice. Thus, a register – a system of long-term clinical monitoring of a patient population – is a significant source of information on effectiveness and safety of medical interventions. This tool of follow-up observation of a patient's condition is irreplaceable in medicine, particularly, in allergology both for epidemiological purposes and to assess effectiveness and safety of therapeutic interventions: e.g., use of IgE antibodies – biopharmaceutical omalizumab.

Keywords: register, long-term follow-up monitoring system, effectiveness, safety, uncontrolled severe persisting bronchial asthma, omalizumab, children.

RANDOMIZED CLINICAL TRIALS AS THE “GOLD STANDARD” OF THE EVIDENCE-BASED MEDICINE

The world medical community around the world has recognized randomized clinical trials (RCTs) as the “gold standard” of the evidence-based medicine [1, 2]. Each medical technology or intervention is evaluated from the perspective of clear evidence of effectiveness, safety and clinical-economic benefits of the use thereof. However, despite all that, RCTs feature a range of certain disadvantages and, unfortunately, do not totally reflect the real clinical practice often enough [2-4].

Let us consider this fact in detail. In order to be involved in one or another RCT, a patient as a trial subject must strictly conform to a range of strictest inclusion criteria. These restrictions (exclusion criteria, to be more accurate) result in the fact that the obtained data are true only for a small group of patients and do not cover patients with concurrent pathologies and other limiting factors. This peculiarity of RCTs may complicate the process of extrapolating observation results to the whole patient population [1-4].

Moreover, in some cases, e.g. due to ethical aspects (especially in neonates and infants), a placebo-controlled trial is infeasible [5].

The same applies to patients with rare pathologies. In such cases small number of ill persons, low disease prevalence and (usually) severe, progressive and incapacitating course of the pathological course render an RCT infeasible.

Formulation of endpoints (both strict and combined) of such trials remains disputable; such endpoints are especially important for pediatric RCTs [5].

Due to high process organization cost, RCTs always have a limited timeframe, whereas detection of most adverse drug effects, as well as of interaction of the drug's combination with other drugs, requires long-term clinical practice of use and observation [6]. Long-term non-experimental trials (cohort, case control and case series trials) could help to resolve this issue. These trials do not feature such stiff restrictions as RCTs, which is why the evidence strength thereof is lower and, despite the fact that they may involve a large number of patients and monitor them for a long time, they have a range of disadvantages: heterogeneity of patient groups, lack of total control over therapy compliance and methodological difficulties complicate real assessment of the obtained results [2, 6-9].

REGISTERS – BASE OF INFORMATION MONITORING SYSTEMS

Thus, registers have recently deservedly become a crucial instrument for improving healthcare quality absolutely necessary both for determining effectiveness and safety of long-term therapy and observation and in case of a rare condition or disease, when a randomized clinical trial is difficult to perform [2, 6, 10, 11].

Epidemiologically, a register (from Late Latin *registrum* – list; Latin *registum* – recorded) is a database of all cases of a certain disease (e.g., an infectious disease) or other pathological conditions related to medical status of a specific population [3, 6, 7]. Thus, the registered cases may serve as an information base for a trial; availability of such a base helps to calculate morbidity parameters. Case monitoring also helps to obtain information and remission and exacerbation of diseases, the prevalence and outcomes thereof [10, 11].

Highly epidemiologically valuable are:

- cancer registers (reports of patients are submitted immediately after diagnosis has first been established);
- twin registers (provided the information necessary to perform trials aimed at identifying genetic and environmental factors in the etiology of various pathological conditions);
- congenital defect registers (intended for registering the abnormalities detected at birth or in the early postnatal period).

These registers are imperfect as they do not take into account stillbirths and congenital disorders, which had not been identified soon after birth: e.g., some congenital heart defects, mental development defects or rare diseases.

Along with that, other types of registers, such as nosological registers (registering specific nosological forms and pathological syndromes), therapeutic registers (providing data on specific types of therapeutic intervention), registers of parameters of the persons subjected to risk factors and local registers (not based on a specific population, e.g., utilizing data of a specific hospital), have been used extensively.

Registers based on the whole population are usually considered the most epidemiologically beneficial; registers based on data of one clinic or on a specific disease may be used a source of cases for case control trials [2].

Thus, a register is a system of clinical monitoring not only of the nosologically similar patients, but also of the employed therapeutic intervention technology from diagnosis to outcome. Use of registers helps to obtain homogenous information by means of a long-term follow-up monitoring of a patient's condition in real practice. Evaluation and analysis of the accumulated data help to achieve clinical, scientific, economic and social objectives [2, 10, 11]. Registers may be retrospective and prospective. Both non-recurrent single registration of specific clinical criteria and long-term monitoring of a patient population are possible.

It ought not to be forgotten that register is a universal information system structure. It is commonly known that any computer program or algorithm consists of a set of specified rules aimed at completing specified actions. Rules conforming to the predefined objective are also used to establish a register. Strict approaches used to accumulate and analyze the obtained results are determined by the predefined objectives.

Dataset for each patient must be homogenous, inclusion of patients – continuous. Registers ought to include all patients meeting the predefined parameters; subjective sampling is unacceptable [2, 10, 11]. Inclusion restrictions must be clearly defined by the register design [12, 13].

Both primary (accumulated specifically for the register) and secondary data may be used as register data sources. The information may be obtained both by means of a direct physical examination of patient and medical documentation analysis (electronic or hard medical records etc.).

One of the most important peculiarities of registers is long-term observation of patients [10-13]. This is a critical condition for analyzing drug effectiveness and safety [6, 9].

Use of registers helps to obtain a sufficiently large representative patient sample. Long-term observation helps to achieve a target amount of endpoints and monitor results for a long period of time.

Registers may include large populations of the patients meeting the predefined criteria; this helps to analyze effect of drug and other therapeutic interventions in a broad spectrum of patients. This predefines one of the important advantages of registers over RCTs, as the latter analyze only specific groups of the so called refined patients, i.e. selected according to strict criteria [2].

As a trial method, unlike RCTs, registers are rather flexible: the purpose of the register may change with time. E.g., an initially established information system aimed at studying safety of a specific drug or other therapeutic intervention may later be used to assess effectiveness of medical technologies or discrimination between different patient subgroups.

Moreover, use of registers helps to analyze healthcare quality – timeliness and completeness of the measures performed, e.g., by means of comparison of the care rendered and current evidence-based recommendations [10].

Registers of some nosological forms and groups of diseases have been well developed and being improved both in the Russian Federation (RF) and abroad [14].

The most widely used registers in the RF are registers of pancreatic diabetes, cardiovascular diseases (acute coronary syndrome, acute myocardial infarction etc.), oncopathology, mucoviscidosis, patients with HIV/AIDS, pediatric incapacitation, congenital disorders etc. The registers primarily valuable epidemiologically for specific nosologies have been supplemented with information systems for monitoring effectiveness and safety of therapeutic interventions [14].

However, these research instruments remain doubtlessly imperfect for allergic diseases.

Registers of allergic diseases

Asthma, allergic rhinitis, atopic dermatitis, food allergy – ca. 20% of the European children suffer from various allergies. Early severe atopic process often continues to persist in adolescence and adulthood [15].

Life quality decrease and total socioeconomic burden of this problem is financially comparable with pancreatic diabetes and rheumatic diseases. Moreover, the problem of immediate allergic reaction – anaphylaxis – to different food components and drugs remain life-threatening [16].

Only several national initiatives (on drug allergy [Pascal Demoly, France, <http://www.dahd.net/>], anaphylaxis [Margitta Worm, Germany, <http://www.anaphylaxie.net>] and chronic hand dermatitis [Christian Apfelbacher, Germany, <http://www.carpe.dermis.net>]) have already been implemented. Such national register projects ought to and may be implemented not only within separate countries, but throughout Europe [15]. The main condition of success of such an initiative is use of a single standardized methodology for optimizing potential benefits of this

instrument not only for clinicians and researchers, but also for patients with allergies: protection of the health thereof throughout Europe regardless of territorial and political barriers.

In 2011, in the context of urgent issues and unimplemented projects, the European Academy of Allergy and Clinical Immunology established a workgroup and formulated the primary objectives – creation of registers of allergic diseases [15]. Initially, this project was aimed at preparing a platform for creating common European registers of allergic diseases without individual territorial borders and developing appropriate monitoring instruments for use both in clinical practice and for research. One of the objectives was to standardize acquisition of data on allergic diseases and, in the end, improve control over allergies and obtain means of managing allergen exposition.

The project is to be focused initially on two national registers of allergic diseases – anaphylaxis (Professor Margitta Worm) and drug allergy registers (Professor Pascal Demoly); after that it is to spread throughout Europe. In the longer term launch of the aimed at analyzing therapeutic interventions is expected: the first will consider local and systemic side effects of immunotherapy (Dr Moises Calderon), the second – use of immunosuppressants in patients with severe atopic dermatitis (Dr Carsten Flohr). The main advantage of this project, which will start simultaneously at several European centers, will be the common methodological approach. Use of biobank data for scientific purposes of all the aforementioned registers has been planned.

Thus, the first four registers will serve as the basis for development of other systems for information monitoring of allergic diseases, especially in respect of methodological aspects – standardized algorithm both of determining data acquisition parameters, formulating endpoints and observing ethical aspects of information use, as well as technical specifications of the programming solution.

Unfortunately, resolution of the Workgroup for registers of allergic diseases of the European Academy of Allergy and Clinical Immunology does not contain any data either on information monitoring systems for patients with bronchial asthma or plans of launching the common register or integrating territorial systems (where present) into the common database.

Bronchial asthma remains a serious public healthcare problem; it affects more than 300 mn patients around the world [16] and is the most common disease of lower airways in children [17]. Asthma usually starts in early childhood and is characterized by different course variants (phenotypes); asthma manifestations may persist for life, especially if severe or concurrent with atopic disease [18-23]. Despite the availability of various guidelines and consensus papers on asthma management, a significant number of patients are not treated adequately, which is why they are unable to control asthma [21-23]. Asthma symptoms are often heterogenous [20-23]. Therefore, it is only natural, that characteristics of patients in clinical practice differ from RCT inclusion criteria; this substantiates the need in evaluating treatment effectiveness and safety in actual practice [24]. Moreover, the asthma control level predefined for inclusion into RCTs is rarely achievable in normal practice.

One of the most effective therapeutic interventions at severe persistent uncontrollable asthma is use of biological agent omalizumab [24-26]. Omalizumab (code ATX R03DX05; lyophilisate for solution for intravenous injections [150 mg]: 1 vial with dosing vehicle) is the only biological drug registered for use at bronchial asthma in over-6 children. It is indicated for children with allergic persistent asthma poorly controlled by other drugs (evidence level B) from therapy stage 3-4 [21, 22]; it considerably alleviates symptoms and decreases the number of exacerbations, improves quality of life and, to a lesser extent, pulmonary function [24-26].

Long-term clinical monitoring is optimal for evaluating effectiveness and safety of omalizumab therapy of severe persistent uncontrollable bronchial asthma (BA) in real practice due to heterogeneity of clinical symptoms in different groups of patients with this disease [24].

Several such projects (Belgium, Mexico, Portugal, Israel etc.) were not large-scale; they were aimed primarily at observing patients with bronchial asthma of varying severity undergoing such a therapy.

Some registers covered only adult patients. Thus, a Belgian 52-weeks-long project involved 158 patients from 35 centers with poorly controllable persistent BA treated with high doses of inhalation glucocorticosteroids together with long-acting β_2 -agonists; 63% of these patients were treated glucocorticosteroids *per os* as additional means of control [27].

An Israeli register also analyzed condition of adult patients with atopic persistent uncontrollable asthma treated with omalizumab in addition to the primary therapy [28]. The secondary data obtained by means of analysis of medical documentation of 33 patients (the average age – 50.0 ± 12.2 years of age; therapy duration – 10.4 months) were used. The analysis demonstrated that the rate of asthma exacerbations and emergency care request significantly decrease in the setting of the performed therapy [28].

In Greece the register of patients with BA treated with omalizumab involved 60 patients under long-term clinical monitoring from 4 centers [29]. Therapy effectiveness was evaluated by the standard (by then) criteria (asthma control level and external respiration parameters, baseline therapy dose and number of exacerbations) after 4 months, 1 year and 4 years in comparison with the initial parameters in the real clinical conditions. The average age of patients was 54 ± 14 years; the inclusion criteria stated that the register involved over-12 children; however, the precise number of children is, unfortunately, not specified. The results obtained by means of this register provide convincing proof that omalizumab's clinical effectiveness registered previously by means of RCTs is quite reproducible in the normal practice [29].

The clinical monitoring project implemented in Germany involved 195 over-12 patients from 85 centers (in total) [30]. All the subjects had a follow-up visit in the 16th week; the researchers managed to monitor condition of 173 (88.7%) patients for 6 months. The obtained results are as follows: reduced number of exacerbations and need in adjunctive therapy, improved FEV₁ and asthma control parameters; this indicates effectiveness and high tolerance to the treatment and confirms the previously obtained positive data; this also allows extrapolating RCT results to the real clinical practice [30].

Moreover, projects of long-term clinical monitoring of patient populations with BA treated with omalizumab (in addition to the baseline treatment) were implemented in Mexico (52 15-67-years-old patients undergoing a 3-years-long therapy course) [31], Italy (142 patients; 1 year) [32], Portugal (15 adult patients; the trial was aimed at identifying short- and long-term [1-2 years] effects of the drug) [33] and Turkey (18 adult patients; course therapy duration varied from 1 to 29 months) [34].

Unlike the aforementioned projects, the Spanish register helped not only to evaluate omalizumab's effectiveness and safety in patients with atopic persistent uncontrollable asthma, but also to compare this group of patients with a group of patients with non-atopic BA in respect of the drug's effect [35]. Evaluation and analysis were based on the data obtained from 29 patients with non-atopic BA (observation period from the beginning of therapy – 27.1 ± 12.3 months), whereas the group of patients with atopic asthma was comprised of 266 subjects (26.8 ± 13.7 months). Parameters of asthma control level, external respiration, general clinical condition evaluation and exacerbation rate were analyzed 4 months and 1 year 2 months after the drug use launch in comparison with the initial condition and between the mentioned groups of patients. Observation results provide convincing proof that omalizumab is effective in patients with non-atopic bronchial asthma as an auxiliary means of achieving control over the disease [35].

Results of a long-term clinical monitoring performed in France [36] involving 104 6-18-years-old children with atopic persistent uncontrollable asthma are especially valuable for clinical practice. All the children were treated with omalizumab (in addition to the baseline therapy; dosage corresponded to the recommendations). Asthma control level, number of clinically significant exacerbations, baseline therapy dosage, expiratory respiration parameters at the treatment onset, in the 20th and the 52nd therapy week were compared with the pre-omalizumab parameters in order to evaluate effectiveness. Observation results indicated effectiveness of the

performed therapy, high tolerance to the drug; the obtained parameters were higher than in a previously performed RCT [36].

Results of a global project (register Experience) aimed at determining effectiveness and safety of severe persistent uncontrollable bronchial asthma therapy that had been being performed in the real practice for 2 years using biological drug omalizumab are doubtlessly important for clinical practice as well [37].

Multicenter information real clinical practice monitoring combined efforts of researchers from various countries: Argentina, Bulgaria, Canada, Cyprus, the Czech Republic, Hungary, Philippines, Portugal, Russia, Slovakia, Slovenia, Spain, the Netherlands, Taiwan.

Effectiveness criteria included general evaluation of treatment effectiveness on the basis of clinical and instrumental examination (in the 16th week); number of clinically significant asthma exacerbations; dynamics of the external respiration parameters; number of absent-from-work/study days; asthma control level; evaluation of asthma episodes by means of the Asthma Control Test (ACT) and/or the Asthma Control Questionnaire (ACQ); evaluation of life quality of patients with bronchial asthma (AQLQ and/or mini-AQLQ); use of oral corticosteroids.

Nature and rate of adverse effects were also analyzed in the register for safety evaluation.

Inclusion period was ca. 2.5 years (from May 2006); post-therapy observation period duration – 2 years. The register was comprised of data on 943 subjects (2 under-12 children, 51 12-17.9-years-old children).

Results of 2-years-long global clinical monitoring Experience demonstrated that use of a biological drug in patients with poorly controlled persistent BA helps to reduce the rate of clinically significant exacerbations (the data obtained 12 and 24 months after the therapy onset as compared to the data obtained 12 months before the treatment onset), alleviates symptoms, improves pulmonary function, asthma episode control and life quality [37]. The performed retrospective analysis demonstrated that the number of patients who had not had clinically significant exacerbations within their 12 months before the treatment onset increased from 6.8 to 54.1 and 67.3% by 12 and 24 months of omalizumab therapy, respectively. The number of symptoms and amount of the emergency drugs used additionally 24 months after the therapy onset reduced more than by 50% in comparison with the initial parameters. The need in *per os* corticosteroid use decreased by 24 months (down to 14.2%) in comparison with the data after 12 months (16.1%) and in the beginning of treatment (28.6%).

Long-term observation performed thanks to the data register confirmed safety of the therapeutic interventions [37]. Moreover, data of the multicenter observation correspond with the results of the previously performed clinical trials [27, 30, 32].

Thus, registers have become an important instrument of determining effectiveness and safety of long-term therapy and observation, a methodological means for healthcare quality analysis, as well as determination and assessment of impact of one or another medical technology on healthcare [38]. Thus, data of the difficult asthma register of the British Thoracic Society helped to determine and assess costs of medical care of patients with severe refractory BA and difficult BA (defined according to criteria of the American Thoracic Society) and analyze factors affecting these costs [38].

CONCLUSION

Use of bronchial asthma registers will resolve not only epidemiological objectives, but will also help to achieve the optimal monitoring endpoints of effectiveness and safety of both innovative high-technology treatment methods and long used therapeutic approaches. Clinical monitoring results will help to improve asthma control, compliance to the prescribed treatment, reduce the disease exacerbation rate and increase life quality of patients and members of the families thereof.

The leading establishment for medical care of children with various nosological forms, syndromes and rare diseases in the Russian Federation – the Scientific Center of Children's

Health – is working on creating a register of pediatric patients with severe persistent uncontrollable bronchial asthma.

System of monitoring patients with bronchial asthma is a necessary condition of improving medical care rendering to patients with BA. Moreover, integration of territorial information systems will help to rationalize and harmonize development and management of patient registers, create a common protected bank of personal medical data of all patients with BA, optimize approaches to health protection and resolve not only scientific, but also clinical objectives.

CONFLICT OF INTEREST

The authors have indicated they have no financial relationships relevant to this article to disclose.

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