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Modern therapies in rheumatology: the role of clinical trials

ABSTRACT

Recent decades have seen an increase in the effectiveness of therapies used. However, there are still many challenges facing modern medicine, including rheumatology. The development of modern therapies is made possible by large-scale clinical trials. Clinical trials are not only designed to verify the effectiveness of a therapy. They are also intended to assess the bioavailability, pharmacodynamics, metabolism, and elimination of therapeutic substances. In Poland, clinical trials have been conducted for many years. It is estimated that the costs currently borne by the sponsors of clinical trials in Poland amount to more than one billion per year. In rheumatology, clinical trials are important not only because of their scientific aspect, but also because they increase the availability of the latest and often most effective therapies for patients. Unfortunately, the availability of therapies under the National Health Fund in Poland is currently low. Thanks to clinical trials, a much higher proportion of patients in Poland have access to the latest generation of biologics and biosimilars based on produced human monoclonal antibodies. Given that new biological therapies can be expected to be registered in the coming years, the number of clinical trials will increase. Therefore, it is currently important to familiarise both doctors and their patients with the subject of clinical trials.

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Modern medicine is constantly looking for new therapies, as it is still unable to effectively help patients suffering from many conditions. Continuous progress in medicine is driven by the development of clinical trials that assess the safety and efficacy of introduced drugs, as well as new medical technologies and nutritional products. A key principle of current clinical trials is the assumption that the priority is to protect the rights of each participant by ensuring their safety. These principles are set out in great detail in the Declaration of Helsinki, which was established in 1964. The basis for obtaining reliable data to bring safe and effective medicines to the market is compliance with current regulations and recommendations of international clinical trial agencies. In Europe, these issues are regulated by the European Medicines Agency (EMA), while in the United States, they are regulated by the Food and Drug Administration (FDA).

A clinical trial is any research conducted in humans (healthy or sick volunteers) with the aim of discovering or confirming the clinical or pharmacological effects of a medicine or treatment. These trials are also conducted to identify adverse effects, assess bioavailability, pharmacodynamics, metabolism, and elimination of medicinal substances. All this leads to the determination of the safety and efficacy of new therapies [1].

The first attempts to conduct tests on humans can be found in the Bible (Book of Ezekiel, 562 BC). It describes the division of men into two groups, where one group was fed a plant-based diet and the other was fed meat.

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As a result of these tests, a vegetarian diet was proven to be healthier. These are the first references in the literature which prove that even in ancient times, people considered what is healthy for us and what is harmful to us [2].

Another example is James Lind, a British-born physician who conducted research among sailors suffering from scurvy. He proved in 1747 that the systematic administration of citrus fruit to scurvy patients could combat the disease [2].

The first clinical trial that already defined inclusion and exclusion criteria took place in 1894. Approximately 160 boys suffering from scarlet fever took part in the experiment and were treated with berry extract [2].

The first randomised trial (randomly assigning a patient to a group) was conducted in 1898. At that time, available therapies were studied in comparison with the pertussis vaccine [2].

Subsequent and more modern research, such as the work on penicillin, led to the need for regulation for clinical trials. One reason for this was the actions of Nazi doctors who tested their therapies on concentration camp prisoners during the Second World War [2].

A great achievement was the creation of the Nuremberg Code, issued in 1947, which stipulated that the patient must voluntarily agree to take part in the trial and the trial must have a scientific basis to be conducted [2].

Clinical trials in Poland have been conducted for many years, both in private centres and in highly specialised hospitals. The beginnings of clinical trials in Poland that are sponsored by foreign pharmaceutical companies date back to 1984. At the present time, the number of trials is increasing. This is related not only to the increasing potential of innovative companies in terms of discovery, creation of new molecules with potential therapeutic value, but also to the reduction of research opportunities in Eastern Europe following the outbreak of war in Ukraine.

Data from 2000–2010 indicate that approximately 400–500 new clinical trials are registered, involving more than 50 000 participants. Clinical trials are usually outsourced to specialised intermediary companies, which handle both the selection of centres, the training of researchers and the organisation and supervision of trials. Expenditure on the implementation of trials is very high, also due to the need to maintain international standards for their reliability and objectivity. The costs borne by clinical trial sponsors in Poland are estimated at more than PLN 1 billion annually.

Nowadays, the most important document to follow when conducting clinical trials is the Good Clinical Practice (GCP). It mainly defines the obligations of the doctor and the sponsor towards the patient. The development of this document has led to a significant improvement in the quality of trials [2].

Today, clinical trials can be divided into several stages:

Phase I clinical trial. A candidate for participation in the first phase of a clinical trial is a healthy volunteer. The exception to this is the oncology trial, where the requirement is that the participant must be an ill person. Its aim is to initially assess the safety of the therapy used. It also examines the mode of absorption, elimination, as well as metabolism, toxicity and interactions with food and other drugs used. At this stage, the dosage of the drug and its efficacy can be predetermined [3].

Phase II clinical trial. If the results of phase I are positive, phase II is planned. Its aim is to answer the question of whether the test drug works in a specific group of patients and whether its use is safe. Phase II involves many more participants than phase I, usually several hundred volunteers. At this stage, the efficacy of the treatment for a given disease is studied, as well as the effect on its remissions and the safety assessment of therapy provided. These trials also feature several arms with different doses of the drug, to which the system qualifies the patient. This phase is also used for assessing dosage, parameters related to bioavailability, metabolism, and elimination of the drug, where the sex of the patient becomes important. In this phase, it is also possible to compare the test substance against a placebo by conducting it using a double-blind trial. In such a trial, neither the researcher nor the patient have information about the therapy being administered [3]. The main goal of phase II is to obtain the most effective and also safest dose of the drug.

Phase III clinical trial. If the risk–benefit ratio is favourable, phase III can be initiated. Phase III is conducted on a much larger scale than phases described so far and may take many years. It involves participants from all over the world and is designed to assess efficacy, safety and confirm the dosing regimen in a much larger study group and over a much longer period of therapy. At this stage, the dose of the drug is usually already estab-

lished and a double-blind method is also used. It is also common to find trials in this phase to compare the test drug with a drug already on the market [3].

Phase IV clinical trial. The final phase of clinical trials is the post-marketing phase. This means that a test substance has been approved for the market. This phase also aims to confirm efficacy and safety of the substance over a very long period of use. Such trials are conducted in a very large population. It is then important to collect and report all information about possible adverse events experienced by trial participants, so that possible risks of the therapy can be detected in the long term [3].

The participation of clinical trial subjects is essential for the development of new drugs. All medicines must undergo clinical trials to be marketed. According to the GCP, the safety and well-being of the patient are more important than the benefit of the clinical trial itself. Patients participate in the trial voluntarily. Every researcher who recruits a patient for a trial is obliged to present all available therapies to the patient before offering them participation in a clinical trial. It should be up to the patient to decide which route they will take [3].

The first step to participate in a clinical trial is to read and sign the informed consent form by the patient. The candidate for the trial should be given enough time to read the document, have the opportunity to ask questions and receive comprehensive answers It is the doctor's task to explain to the patient in a very detailed and understandable way how the entire trial will proceed and to define the patient's responsibilities. The consent is signed in two identical copies, one of which is given to the patient. It is also important to note that the clinical trial participant may withdraw from the trial at any time without giving any reason. The doctor should make sure that the candidate understands that it is still a medical experiment that does not guarantee any direct health benefits. At this stage, all the risks associated with participation in a trial should also be discussed with the patient.

The doctor's task is also to inform the patient about the purpose of a trial and the results of its previous phases [4].

To include a patient in a clinical trial, the patient must meet all inclusion criteria and not meet any exclusion criteria. These criteria are defined by each clinical trial protocol. Once the patient is eligible, the period of use of a given therapy begins. During this time, the patient attends scheduled visits at the research centre, where not only their health status but also their mental state is monitored. The participant's personal data are confidential and trial results are reported under a participant number. No data regarding their health status may appear under their name and surname.

The patient in a clinical trial is not entitled to any costs associated with their participation. Apart from the phase I conducted in healthy volunteers, the patient is not entitled to receive any financial compensation for participating in the trial either. They will only be able to receive compensation for the costs associated with their visits [4].

Clinical trials are carried out in research centres specially designed for this purpose. These facilities are equipped with certified medical equipment and are staffed by specialised personnel: medical, nursing, and administrative staff. All trials are conducted with the highest quality standards. Developed procedures, periodic checks and audits ensure patient safety and guarantee the acquisition of reliable data.

In addition to the GCP, the bodies that are responsible for supervising and reviewing clinical trials in Poland are the Office for the Registration of Medicinal Products, Medical Devices and Biocidal Products and the Bioethics Committees that review and monitor the progress of the trials. All of this is to ensure both the safety and protection of the rights of clinical trial participants.

The underlying causes of rheumatic diseases are increasingly well understood. Understanding the pathogenesis of diseases allows the use of targeted therapies that are designed to target the cause of the disease. The most up-to-date and effective treatment method is drug therapy with biologic disease-modifying drugs (bDMARDs) and innovative therapies using targeted synthetic disease-modifying drugs (tsDMARDs), which are considered to be among the most advanced methods of treatment in the world. Biological therapy in rheumatology has been used worldwide for over 20 years; however, it is not easily accessible to all those in need due to its high cost.

Biological therapies based on the use of drugs produced by molecular biological engineering are the most commonly used. The mechanism of action of these medications is very precise and effectively inhibits the progression of the disease as well as the destruction of peripheral joints or spine.

The development of these drugs was made possible by identifying and isolating the main pro-inflammatory proteins (cytokines) involved in inflammatory processes. Based on these discoveries, appropriate monoclonal antibodies and fusion proteins were produced. In practice, this means that it has become possible to block specific cytokines and thus the inflammatory process [3].

The latest generation of biologics is based on produced human monoclonal antibodies. Older medications contained immunoglobulin fragments taken from mice (chimeric biologics). Currently, there are many pharmaceuticals available on the market, mostly "fully human", both for use as monotherapy and in combination treatment with classic disease-modifying drugs, most commonly methotrexate.

The strong anti-inflammatory effects of these medications were confirmed in numerous clinical trials. After treatment with these drugs, inflammatory symptoms in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) are significantly reduced or disappear. As a result of the treatment, patients do not suffer from joint swelling and joint pain, peripheral joint destruction and spinal bone destruction are halted, the mobility of bone structures and their quality of life improve.

Biologic medications are administered intravenously or subcutaneously, while innovative drugs are administered orally. Subcutaneous pharmaceuticals are administered at intervals of one, two, three or four weeks. The frequency depends on the type of drug and individual course of disease. Patients receive oral medicines in tablet form on a daily basis. Biologic medications used in rheumatology include the following inhibitors: interleukin inhibitors — IL-1, IL-6, IL-12, IL-17, IL-23, tumour necrosis factor α (TNF-α) inhibitors, B-CD20 lymphocyte inhibitors, T-lymphocyte costimulation inhibitors, which modulate CD28 lymphocyte stimulation.

The basic pharmacological treatment of inflammatory rheumatic diseases is thus based on DMARDs that suppress the symptoms of inflammation, prevent or delay the onset of destructive lesions in the joints, resulting in low disease activity or even remission. These drugs are divided into synthetic drugs, with a distinction made between conventional drugs, i.e. classic synthetic drugs (csDMARDs), such as metotrecasate, leflunomide, sulphasalazine, chloroquine, hydroxychloroquine, and targeted synthetic drugs (tsDMARDs), such as Janus activated kinases (JAK) inhibitors and apremilast, and biologics, which can be divided into originals and biosimilars. Biologic DMARDs (bDMARDs) include anti-cytokine and non-cytokine therapies, distinguished by a different mechanism of action. Currently, anti-cytokine biological therapies in rheumatology include treatment with the above-mentioned inhibitors of pro-inflammatory cytokines, particularly against IL-1, IL-6, IL-17, IL-23 and TNF-α, which are human monoclonal antibodies, either humanised or chimeric, and fusion proteins. These include adalimumab, anakinra, certolizumab, etanercept, golimumab and infliximab.

Moreover, drugs with a mechanism of action other than anti-cytokine — which act on B-lymphocyte receptors and modulate T-lymphocyte function — are used and include rituximab and abatacept, respectively.

These csDMARDs include JAK inhibitors baricitinib, fligotinib, tofacitinib, upadacitinib and apremilast.

Targeted synthetic DMARDs (tsDMARDs) show efficacy in the treatment of both cancer patients and those with autoimmune diseases. They work by blocking the inflammatory process induced by a variety of pro-inflammatory cytokines, and the mechanism of drug action involves the inside of the cell.

Biologics and innovative drugs have contributed to a major breakthrough in medicine. Thanks to them, achieving stable remission in the treatment process has become a realistic goal that is achievable by patients and doctors for the first time.

These therapies have resulted in significant advances in the treatment of many autoimmune diseases and cancers. They have applications in many fields of medicine, including rheumatology, dermatology, gastroenterology, pulmonology, diabetology, neurology, haematology, and oncology.

Unfortunately, a major problem is still the high cost of biological and innovative therapies, which limits their availability.

The first biologics in rheumatology belonged to the TNF-α group, which initially found clinical use in anti-cancer therapy, followed by rituximab — a monoclonal antibody that received approval in 1997 for lymphoma treatment.

Rituximab was registered for use in RA in 2006. Today it is used in:
— chronic lymphocytic leukaemia;
— non-Hodgkin's lymphomas;
— acute lymphoblastic leukaemia;
— cutaneous T-cell lymphoma;
— granulomatosis with polyangiitis and microscopic polyangiitis;
— RA.

The next drug approved was the fusion protein — etanercept. At a similar time, infliximab — a chimeric monoclonal antibody — was also approved.

In 2002, another drug called adalimumab was registered for use in RA, which in subsequent years received indications for PsA, Crohn's disease, ulcerative colitis, active polyarticular juvenile idiopathic arthritis (JIA), arthritis with associated enthesitis, psoriasis vulgaris, AS, inflammatory axial spondyloarthropathy without radiographic changes, hidradenitis suppurativa, uveitis, uveitis in children and adolescents.

Cetrolizumab pegol was also approved for administration in Crohn's disease in 2006 and RA in 2008. This monoclonal antibody is used in combination with methotrexate or as monotherapy for the treatment of RA, Crohn's disease, plaque psoriasis, PsA and various forms of inflammatory spondyloarthropathies (SpAs).

In 2008, golimumab, a human monoclonal antibody, was also approved. Today, it is used in RA, JIA, PsA, AS, axial SpA without radiographic changes, ulcerative colitis.

Tumour necrosis factor α drugs were followed by IL-6 blocking drugs. In 2007, tocilizumab — a monoclonal antibody against IL-6 — was approved for marketing. Tocilizumab is used in patients suffering from RA, JIA, central serous retinopathy, cancer associated retinopathy, COVID-19. It can be used in combination with methotrexate and as monotherapy in both children and adults. Tocilizumab is the only drug that is currently approved in two forms (subcutaneous injection and intravenous infusion). It has been categorised as a first-choice drug along with TNF-α inhibitors and scDMARDs from the JAK inhibitor group in RA. The drug was found to be effective in many patients after failure of TNF-α inhibitor therapy. Other drugs affecting IL-6 include olokizumab, sarilumab and sirukumab, however, they are not yet available in Poland.

Another breakthrough came with interleukin 17 (IL-17A) inhibitors and the drug secukinumab that was approved in 2015. Secukinumab is a human recombinant monoclonal antibody belonging to the IgG/κ class obtained by expression in Chinese hamster ovary cells for the treatment of uveitis, RA, PsA, AS, SpA and psoriasis.

Iksekizumab, a recombinant monoclonal antibody against IL-17RA, is a humanised monoclonal antibody used for the treatment of autoimmune diseases. It was approved as a substance for medical use by the FDA in March 2016 and a month later by the EMA. Currently, iksekizumab is used in dermatology, venereology, and rheumatology for indications similar to secukinumab.

Another drug is bimekizumab, a monoclonal antibody — a protein designed to combine with the IL-17A, IL-17F and IL-17AF interleukins which are messenger molecules in the body's immune system (the body's natural defence mechanism). It is currently used in adults for the treatment of plaque psoriasis. It is awaiting registration for use in PsA. Clinical trials in this area are currently underway.

Another drug is Guselkumab, a human IgG1λ monoclonal antibody that binds to IL-23. Guselkumab received FDA approval in July 2017 for the treatment of plaque psoriasis and was approved in April 2018 for the treatment of PsA in Japan. In July 2020, the FDA approved Guselkumab as the first IL-23 inhibitor for the treatment of active PsA in the USA.

In addition to biologics, there is another previously mentioned group of drugs — tsDMARDs from the JAK inhibitor group, e.g. tofacitinib, baricitinib, upadacitinib, fligotinib.

The FDA approved tofacitinib in 2012 while the EMA in 2017. Today, tofacitinib is used in the treatment of RA, PsA, ulcerative colitis, AS, and JIA. It can be used as monotherapy or in combination with methotrexate.

Another tsDMARD from the JAK inhibitor group is baricitinib, introduced to the market in 2017 for indications such as RA when DMARD therapy is ineffective or impossible to use in a given patient, for the treatment of atopic dermatitis (AD), and severe plaque psoriasis. In 2020, the FDA approved the use of baricitinib in the fight against the COVID-19 pandemic. Currently, trial are currently underway for baricitinib in systemic lupus erythematosus (SLE).

Another tsDMARD from the JAK inhibitor group is upadacitinib, which was approved by the EMA on 17 October 2019. The drug is used in RA, PsA, AS, AD and ulcerative colitis.

In clinical trials, it showed greater efficacy in RA patients compared to adalimumab.

The most recent approved tsDMARD from the JAK inhibitor group is filgotinib for patients with RA and ulcerative colitis. In November 2011, results from a phase II trial in RA patients were published, where half of the treated patients experienced complete (or near complete) remission of the disease. In September 2020, filgotinib received its first approvals in the European Union and Japan.

Apremilast was approved by the FDA in 2014 for patients with active PsA and moderate to severe plaque psoriasis. It received approval for the treatment of oral ulceration in 2019. In the European Union, it was approved for marketing in January 2015.

On 14 February 2022, a marketing authorisation was granted for anifrolumab, which blocks the biological activity of type I interferon, for the treatment of SLE patients. Several clinical trials with this molecule are also currently underway in systemic sclerosis and trials are planned for polymyositis.

Another group of drugs are Bruton's tyrosine kinases, whose function is to transduce signals from various cell surface receptors, most notably B-lymphocyte receptors. They are currently used in cancer patients. Studies conducted over the past 30 years have revealed that their action against cancer cells is more selective than classical cytostatics. Specific Bruton's tyrosine kinases inhibitors, including ibrutinib and acalabrutinib, are currently used in lymphoma, chronic lymphocytic leukemia, and Waldenström's macroglobulinemia.

Nintedanib (a tyrosine kinase inhibitor), which is used in rheumatology in addition to oncology, was approved on 15 October 2014 for the treatment of idiopathic pulmonary fibrosis in the United States. In the European Union, nintedanib was approved on 27 November 2014 for the treatment of lung cancer and on 19 January 2015 for the treatment of idiopathic pulmonary fibrosis.

In 2012, the EMA also defined biosimilars as similar medicinal products to those already approved, which have a similar efficacy and safety profile and are used for the treatment of the same conditions. There have been a lot of clinical trials conducted with this group of drugs. There is ample evidence from clinical trials that biosimilars are as effective and as safe as the originals. Biosimilars are also more efficient from an economic point of view, as they allow a much larger group of patients to be treated for a much lower cost. As a result, patient access to biological therapy increased significantly in 2021. Currently, patients have access to biosimilars under the National Health Fund (NHF) drug programme. An example is a drug called Riximyo (a biosimilar to rituximab), which was included in the drug programme for RA patients on 1 November 2021. Another such example is Imraldi, a biosimilar to adalimumab, which has been reimbursed by the NHF since 1 January 2022.

The COVID-19 pandemic strongly affected the development of new drugs. Many early phase trials were halted with the onset of the pandemic. The focus was on the search for and production of vaccines against COVID-19. The search has also begun for drugs already approved to fight the pandemic, such as tocilizumab.

Currently, clinical trials are also based on finding new indications for already registered drugs. An example is baricitinib and several clinical trials that are currently underway in SLE. Moreover, there are several clinical trials in oncology and rheumatology involving tyrosine kinase inhibitors. Due to their mechanism of action, many drugs are equally effective in the treatment of other autoimmune diseases associated with rheumatic diseases such as psoriasis or inflammatory bowel disease. The search for new indications for JAK inhibitor drugs, whose oral route of administration is also important in many cases, also provides opportunities for more effective treatment — this is particularly relevant for the treatment of children.

The pandemic is estimated to have slowed the development of new drug therapies by five years. In rheumatology, we can only focus on current opportunities and observe the results of the latest clinical trials.

According to current guidelines in Poland, biological treatment is not the first line of treatment. Treatment of the patient starts with csDMARDs. When csDMARDs do not bring improvement or they cause side effects, the patient is eligible for biological therapies or the treatment with newer-generation synthetic drugs.

Currently in Poland, only a few per cent of rheumatology patients are treated with biologics, while in other European countries, biologics or JAK inhibitors are part of routine therapeutic management. Approximately 30% of patients in the European Union benefit from biologics.

Only approximately 1.8% of RA patients in Poland benefit from the drug programme [5]. Overall, less than 2% of patients benefit from drug programmes for rheumatic diseases [5]. In other countries, this percentage is estimated to be in the range of 15–20%, and biologics are available on prescription in pharmacies in, among others, Austria, Belgium, Bulgaria, Czech Republic, Finland, Germany, Ireland, Slovenia, Sweden, Latvia and Lithuania. The reason for the poor availability of biological therapies in Poland is attributed to time-consuming and demanding criteria for patient eligibility for treatment.

Currently, biological therapy is available as part of NHF treatment. The Ministry of Health's drug programmes include B.33, B.35, B.36, B.75 and B.82.

In Poland, clinical trials have a significant effect on increasing patient access to modern therapies. As part of clinical trials, the patient receives free medical care and the opportunity for state-of-the-art treatment.

Early initiation of correct treatment gives patients the opportunity for disease remission and improved quality of life. The lack of availability of medicines results in a poor prognosis and a series of consequences, including disease progression. Both patients and doctors hope that more drugs will be reimbursed in the coming years. Currently, we are awaiting further positive decisions from the Minister of Health on this issue.

Currently, guselkumab, filgotinib and anifrolumab are awaiting approval for a drug programme in rheumatology: guselkumab for the treatment of PsA, fligotinib for the treatment of RA, and anifrolumab for the treatment of SLE patients.

According to projections for the number of newly registered biological therapies per year, there is an estimated increase from 13 molecules in 2014–2018 to 27 molecules in 2021––2025 — Institute Spotlight on Biosimilars, an IQVIA report on biological therapies. This value is likely to be marked by a continuing upward trend.

CONFLICT OF INTEREST

None declared.

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