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Compliance, adherence and *concordance* in the practice of a rheumatologist. Effectiveness of the therapeutic plan: determinants and possibilities for improvement

ABSTRACT

Progress in the treatment of rheumatic diseases is associated with the use of drugs focused on modifying disease mechanisms, which in turn leads to a significant improvement in health. Modern treatment is also associated with reducing the risk of disability and exclusion from important social roles. New drugs, including biological drugs, are expensive and require compliance with the regime related to their use. The above-mentioned factors make it necessary to change attitudes and to strengthen the patient's motivation to comply with medical recommendations. The paper presents a terminological base in the field of compliance, adherence, concordance and persistence. Moreover, factors limiting compliance with recommendations in the case of chronic diseases were indicated, as well as methods of measuring compliance and adherence, both objective and subjective. It was also shown that the pandemic situation significantly reduced the readiness of patients to comply with therapeutic recommendations, which requires a redefinition of the model of cooperation between the doctor and the patient, and numerous methods of facilitating adherence have been proposed.

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KEY WORDS: *compliance; adherence; concordance; persistence*; rheumatic diseases; biological agents

INTRODUCTION

The late 1980s brought a qualitatively significant evolution in the treatment of rheumatic diseases, with the introduction of disease slowing/modifying anti-rheumatic drugs (DMARDs). Unfortunately, observations showed that DMARDs, on the one hand, provided significant benefit to patients, but, on the other hand, were not well tolerated by patients, as they have significant side effects. Hope came with the discovery of methotrexate (MTX). However, methotrexate was not an ideal solution, as patients could not discontinue therapy and, in some of them, disease activity persisted despite treatment. Methotrexate could also not be used in women planning pregnancy, and in people who regularly drink alcohol [1, 2].

A milestone in the care of rheumatic patients was the discovery of biologic disease-modifying anti-rheumatic drugs (bDMARDs) in the late 20th century. The emergence of biological drugs is the result of years of research into the course of autoimmune processes leading to pathological structural changes in joints. Inhibitors of the pro-inflammatory cytokine TNF-α were the first to emerge. This factor plays both a protective role against infections and tumours and also plays an important role in the development of the inflammatory

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process of the synovial membrane, leading to joint destruction [3].

Due to the rapidly advancing developments in the therapeutic management of rheumatic diseases, EULAR has decided to update the nomenclature of available therapies. Medicines obtained by chemical synthesis, i.e. methotrexate, sulphasalazine or leflunomide have been given the status of conventional disease-modifying anti-rheumatic drugs (conventional synthetic DMARDs, csDMARDs), and JAK3 inhibitors received the status of targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs). Original biologics are defined as biological disease-modifying anti-rheumatic drugs (bDMARDs) and their biosimilar counterparts as bsDMARDs [3].

Currently, in the choice of management in the treatment of rheumatic diseases, a very important role is played by the therapeutic goals set and agreed by the doctor and the patient. Introduced drugs that modify the course of the disease make it possible to achieve remission or low disease activity. Scientific societies and other organisations define the endpoints of therapy, the conditions for achieving remission, the conditions for terminating therapy and, on the basis of clinical studies, prepare recommendations for the use of drugs, also in dual therapy or poly-therapy regimens, or for the use of these drugs in emergency conditions — infection with the SARS Cov-2 virus or vaccination.

However, for many patients, recovery is not about achieving specific scores on the DAS or BASDAI scales but about freedom from pain, keeping/improving mobility, staying in employment, continuing and taking on new life roles or social roles. Women want to be mothers, they want to be involved in caring for grandchildren, people with diseases want to play sports, etc. Therefore, also in line with EULAR recommendations, treatment is not only about pain relief — although very important and one of the priorities — but it also requires a holistic approach focusing on all aspects of the disease. Such possibilities are offered by biological treatment; however, it imposes demanding requirements both on the doctor (qualification and introduction to the programme) and on the patient (compliance with recommendations, follow-up examinations). In order to achieve the ambitious goals described above, cooperation between the doctor and the patient is necessary. This helps the patient to understand the treatment procedure and comply with therapeutic recommendations, not only related to the use of drugs, check-ups, but also to changes in lifestyle, physical activity, diet, mental hygiene, *etc.* [4].

People with rheumatic diseases often are multimorbid. The involvement of several specialists in the treatment process, use of multiple drugs and often polypharmacy are reasons for the increased frequency of drug problems [5], which clearly necessitates cooperation between specialists and the patient. This cooperation, therefore, allows and helps to identify and solve current drug problems and to prevent potential problems from becoming real ones. One of these problems is medication adherence.

COMPLIANCE, ADHERENCE, CONCORDANCE, PERSISTENCE

The terminology of *compliance*, *adherence*, *concordance*, and *persistence* was introduced to organise the therapeutic model and the involvement of the patient and physician in the treatment process.

COMPLIANCE

This concept implies passive participation of the treated person, consisting only of compliance with the recommendations of the treating physician. *Compliance* is also referred to when the therapeutic regimen determined by the manufacturer or scientific society indicates the therapeutic doses of drugs, the method of administration of preparations or the frequency and time of administration [6, 7]. The first *compliance* recommendation in the management strategy for patients with RA is to include csDMARD treatment as soon as possible after diagnosis. Treatment is continued and intensified rapidly enough to achieve the treatment goal of sustained (lasting at least 6 months) remission or low disease activity [8].

Compliance also includes agreement on the frequency of visits to the rheumatologist, the frequency of check-ups which are important in deciding whether to continue the agreed treatment regimen or whether to change it. EULAR recommends visits every 1–3 months. In the absence of improvement after 3 months of treatment and/or failure to achieve remission after 6 months, treatment should be modified (recommendation 3) [6, 8, 9].

Unfortunately, in long-term treatment, *compliance* often fails. Disruptions to *compliance* are determined by many factors, not

only the lack of satisfactory improvement in health [5, 9].

ADHERENCE

This term refers to the patient's adherence to the therapeutic plan. For this to occur, the patient must understand the purposefulness of the diagnostic and therapeutic actions, which promotes their acceptance and improves the effectiveness of therapy [6, 7]. Conscious cooperation based on the partnership of both parties is necessary here — a change in the patient's attitude from a passive one (expecting the doctor to cure the affected part of the body) to an active one (conscious actions towards health improvement). The management strategy is agreed with the party that is the most concerned, i.e. the chronic patient him or herself. Therefore, in addition to the requested tests, it becomes crucial to build contact and trust with the patient and to talk. During subsequent visits, the therapeutic goal is agreed on the basis of objective premises and the patient's expectations. Collaborative decision-making about treatment between patient and rheumatologist should cover important aspects of the disease: information about the disease itself and the risk of disability entailed by the disease, standardised assessments of activity and disease progression. The doctor determines, together with the patient, the aim of the treatment, how it will be achieved, available forms of treatment, forms of medication, the ways in which it is administered; the benefits and risks of the various therapies are also discussed. The patient becomes a partner for the doctor and the doctor has time for the patient with the conviction that the „investment" in conversation will become the basis for good cooperation and adherence to the treatment regime for years. Especially since biological therapies, particularly with innovative drugs, are very expensive [7].

The economic aspect referred to at this point relates to the patient's activity and his or her ability to undertake gainful employment, as well as to pharmacoeconomics. This is because there is a high probability that the rapid initiation of innovative disease-modifying treatment will quickly lead to remission and the patient will be able to return to work and relieve the health care system of expenses [9].

CONCORDANCE

This concept means building an understanding with the doctor, where the patient is the active party. An approach that involves *concordance* focuses on the relationship and interaction between patient and physician [6, 7]. *Concordance* aims at the patient's understanding of the purposefulness of the diagnostic and therapeutic measures, reinforces his or her approval and involvement. The beliefs and preferences of the doctor and the patient are fully taken into account, with the assumption that the patient is the one who matters the most, that the patient and his or her needs are the focus of attention. The patient remains at the centre, with his or her needs, including psychological needs (not every patient is ready for innovative treatment at a certain point in life), family situation, economic situation, etc. [10]. The doctor understands the patient's limitations in this regard and responds to their needs. He or she supports the patient in decision-making regarding treatment, encourages changes in lifestyle, as well as changes in psychological functioning. In the *concordance* model, it is assumed that a medical consultation is a negotiation between equal partners: doctor and patient [11]. *Concordance* also increasingly refers to the broader concept of patient support with taking medications (Horne). Therefore, *concordance* is a negotiation, a conversation enabling agreement on a therapeutic plan of which the patient is convinced, which he or she understands, accepts, co-develops and modifies with the doctor. It is also a form of support provided to the patient to help him or her adapt to the limitations related to the treatment. The patient remains the focus but is proactive, engaged, collaborative and responsible. *Concordance* is a challenge for both the patient and the doctor. Thus, *adherence* to the therapeutic plan is largely effective when *concordance* occurs. It is, therefore, possible in an innovative approach to therapy to reverse the order - the doctor-patient encounter should begin by building a *concordance* relationship. Treating the patient as an equal partner is a point of departure for therapeutic dialogue, which ensures *adherence* and is a guarantee of *compliance* also in the long term [10, 11].

PERSISTENCE

This concept means not interrupting therapy, i.e. persisting with the prescribed therapy [6, 7, 11].

World Health Organization: in developed countries only about 50% of patients with chronic diseases follow the recommendations,

in Poland up to 65% of chronically ill patients do not follow the recommendations [7, 12].

Dworakowska et al. point to three dimensions of treatment *persistence* — initiation, implementation and discontinuation of therapy [13].

1. *Initiation* of treatment — the patient may fail to comply with therapeutic recommendations already at the stage of filling a new prescription or delay the decision to fill the prescription; this may be related to cost, the belief that the use of the medicine is harmful or has adverse effects, where this knowledge is naïve, often accidental.
2. *Implementation* of therapy — irregularities in taking medications may occur at this stage (e.g. forgetting to take the medicine, changing doses, taking the medicine at the wrong time). Non-adherence to the recommended dosage and skipping doses may be conscious and intentional or involuntary and accidental, and may also result from the patient's cognitive difficulties [6].
3. *Discontinuation* of therapy — the patient no longer takes prescribed doses of the drug. Often the patient comes to a conclusion that there has been sufficient improvement, or that the therapy does not have the expected effect, or the balance between the cost and the benefits associated with the use of the preparation is unfavourable [13, 14].

According to Dworakowska et al., the following situations may occur at stage 2:

— „white coat" adherence (initially the patient takes medication irregularly, but improvement in regularity occurs a few days before the medical appointment [13];
— „car park" adherence (the patient, wanting to make up for previous neglect, takes larger doses or at shorter intervals before visiting the doctor) [13];
— drug holidays (the patient takes a break after the initial regular intake because he or she comes to a conclusion that there has already been a significant improvement in his or her health; after the break, he or she may or may not return to adherence to the treatment recommendations) [15].

Non-adherence to treatment recommendations is a problem in all chronic diseases. The multicentre study *Prospective Registry Evaluating Myocardial Infarction: Event and Recovery* (PREMIER) showed that poor implementation of the therapeutic plan by patients who had myocardial infarction is the most important reason for the limited efficacy of treatment. One month after leaving the hospital with a recommendation to take acetylsalicylic acid, a β-blocker and a statin, 12% of patients discontinued all three drugs, 14% two drugs and 18% one drug. In patients who completely discontinued medication, one-year survival was significantly shorter (88.5% *vs.* 97.7%) compared with those who continued therapy [16].

In another study involving 112,092 patients without known cardiovascular disease who received statin treatment between 1999 and 2004, 55% did not take the prescribed medication, but among those who complied with medical advice, the rate of cerebrovascular incidents was significantly lower than in the others (RR: 0.74; 95% CI 0.65–0.84) [17].

The results of the analyses concerning the treatment of rheumatoid arthritis, where a significantly smaller group of respondents participated, noted that interruptions in methotrexate treatment were observed among the analysed group of patients. Interruptions in intake were reported by 71 people, or 63% of the total study population. Seventy per cent of patients reported 1–4 missed doses per year, and 16% reported more than 8 such missed doses. Treatment interruptions usually lasted less than 1 month (72%), but as many as 14% of patients discontinued the drug contrary to treatment recommendations for more than 2 months [18].

The World Health Organization (WHO), in operationalising the terms, points out that *compliance* and *adherence* is the extent to which a patient's behaviour (taking medication, following an appropriate diet, changing lifestyle) remains consistent with generally established guidelines. Pharmacological non-adherence includes skipping doses of a medicine, taking a medicine differently from the prescription (increasing or decreasing the dose), discontinuing a medicine too early (low *persistence*), changing medication times, taking medicines that are outdated, damaged or prescribed for someone else, and taking medicines with unadvised products [7].

The US FDA (Food and Drug Administration) also indicates that *compliance* and *adherence* remain very important for hospital and post-hospital care. According to FDA reports, about 60% of patients in post-hospital care have problems naming the drugs they are taking, 30–50% of patients do not strictly follow their doctor's instructions, and about 20% of patients use drugs not prescribed to them. It is assumed that up to half of patients on chronic medication are *non-adherent* patients. It is

Table 1. Factors of non-adherence and discontinuation of therapy [24]

Patient-dependent	Therapy-dependent	Treatment staff-dependent	Socioeconomic
Forgetting Health beliefs Non-*adherence* in the past Addictions	Dosage frequency Evening dose Adverse drug reactions	Ineffective communication with the doctor Poor *concordance* Poorly planned post-hospital care	Socio-economic status Poor social functioning Social background

estimated that these patients may have up to twice the risk of death compared to patients with high *adherence* [19].

On the other hand, patients who adhere to medical advice pay more attention to their lifestyle, including diet and eating habits, physical activity, and higher regularity of contact with the doctor and participation in preventive examinations. In the European Union, 194,500 deaths per year are attributed to drug abuse or poor *adherence*, and the annual cost of non-adherence to medical advice is estimated at 125 thousand million euro [20].

In Poland, the costs of non-adherence to therapeutic recommendations for the public health care system can be estimated at nearly PLN 6 thousand million per year, which is approximately what the National Health Fund spends on providing care by family doctors for the entire population of the country [21].

Pharmaceutical industry costs (opportunity costs) associated with poor *adherence* are estimated to be close to USD 30 thousand million per year [22].

According to WHO, there are 5 groups of factors that can significantly affect *compliance* (source: [7]):
— socio-economic factors;
— factors related to the health care system;
— factors related to health;
— factors related to the applied therapy;
— patient-dependent factors.

Jasińska et al. also provide numerous reasons for *non-adherence* in the course of chronic diseases (source: [6, 7]):
— long treatment time, chronic disease,
— asymptomatic disease,
— the patient disagrees with the diagnosis and/or the treatment provided,
— the patient does not notice the effects of the treatment,
— polypragmasy,
— language barrier when talking to the doctor or pharmacist — the patient does not understand the information
— obtained from the doctor,
— dosage patterns that are difficult to remember,
— fear of side effects,
— the occurrence of side effects,
— the patient does not pay much attention to his or her health,
— loneliness,
— mental illnesses (e.g. depression),
— memory problems,
— dementia,
— high cost of prescribed pharmacotherapy.

At the pharmacy level, *non-adherence* is influenced by (source: [23]):
— failure to correct the patient's incorrect behaviour,
— pharmacist's enigmatic answers or providing no answers to questions asked by the patient,
— issuing substitutes for the patient's regular medication without consulting
— with the doctor,
— too high price of medication, leading to prescriptions not being filled or being filled
— partially,
— losing a prescription.

Factors of non-adherence to treatment can include patient-dependent factors, therapy-dependent factors, treatment staff-dependent factors, and socioeconomic factors (Table 1).

Adherence status requires objective and subjective assessment. This concerns the factors conducive to non-adherence described above, as well as objective and subjective verification of compliance with recommendations in chronically ill patients [6].

Direct methods include direct observation of the therapeutic process by the physician, use of available diagnostic tools, e.g. assessment of the concentration of active substances in body fluids, assessment of the concentration of metabolites in body fluids, assessment of disease markers and their changes. All these methods are available to the attending physician and are used depending on *compliance* or in case of suspicion of non-compliance with adequate treatment.

Indirect methods include the analysis of questionnaires completed by patients or their carers. In addition, it is possible to count tablets in packages of medicines returned by

Table 2. Morisky-Green Test [25]

Question
How often do you skip taking a drug? Do you ever fail to take your medication on time? Do you skip the next dose of medication if you feel well? 1/2/3/4/5 5 — never 4 — rarely 3 — sometimes 2 — often 1 — very often

patients, analyse pharmacy registers or, according to a more modern method, use electronic devices to monitor each time a container is opened.

Indirect methods also include an assessment of the patient's response to the pharmacotherapy applied and their knowledge and experience of taking medication. The doctor also has at his or her disposal indirect methods of assessment relating to the patient's state of health, e.g. assessment of body functions originally disturbed by the disease process, assessment of the structure of a particular organ using available methods (ultrasound examination of the affected joint).

It is worth noting that patients prefer to take their medication in the morning and for such regimens, *adherence* is highest.

Questionnaire methods are also being developed to assess the level of adherence. One of these is the Morisky-Green Test (Table 2).

Studies show that the best results in terms of *adherence* were observed in patients treated for:

— hypotension (72.3% of patients with MPR ≥ 80%),
— hypothyroidism (68.4%),
— type II diabetes (65.4% of patients with MPR ≥ 80%),
— hypercholesterolemia (54.8%),
— osteoporosis (51.2%),
— gout (36.8%) [26, 27].

It is indicated that in acute and life-threatening conditions the index should not be lower than 95%, in hospital conditions even 100%. In others, it should not decrease to values lower than 80% [6]. Unfortunately, data indicate that in chronic diseases, 1/6 of the chronically ill take the prescribed medication sporadically or not at all [28].

Interestingly, it is common for non-*adherence* patients to try to appear disciplined in the doctor's office [28].

From the perspective of the treatment of rheumatic diseases (taking into account the epidemiology), it is optimistic that the most disciplined group of patients in adhering to the recommendations in the above-mentioned study were elderly patients (over 70 years of age), and the least disciplined were young people aged 18–29 years [26].

IMPROVING *ADHERENCE*

Improvement of *adherence* seems, at least in the first stage, quite simple; it is worth paying attention to simplifying dosing regimens, increasing the regularity of medical visits and obligating the patient in this respect, identifying risk factors for non-*adherence* during the medical visit [29].

The key to *adherence* as already indicated in this paper would also be to strengthen *concordance*, improve communication between the patient and those who make up the therapeutic team, including the doctor and pharmacist (*concordance*) [29]. Sometimes patients are more likely to share their doubts about treatment with a nurse who has more time than with a doctor. Increasing awareness and sensitising nursing staff to potential drug problems is therefore worth considering.

CSR activities of pharmaceutical companies also support patient education, including by supporting the activities of patient organisations. Indeed, it is critical to *adherence* to make the patient aware of the impact of the level of adherence on the success of pharmacotherapy, ensuring family support for the patient if necessary.

Educational activities should be undertaken as early as at the time of diagnosis and when the first therapeutic recommendations are given to the patient [6].

THE PANDEMIC

The health consequences of the COVID-19 epidemic concern not only the health losses of COVID-19 patients but also neglected treatment of chronic diseases, weakened *concordance* with the treating physician and non-*adherence*. This is, among other reasons, due to the restrictions introduced on face-to-face visits, difficulties in follow-up examinations, etc. Patients also reduced their physical activity due to the pandemic, which could lead to the development and exacerbation of musculoskeletal pain. Due to limited access to

physicians, many patients may have attempted to modify pharmacotherapy on their own, which is why the safety of prescribed analgesics is now even more important [30].

Mobile applications can be a solution, or at least they could support other solutions. Health apps seem to be a promising strategy for health promotion, a tool for monitoring, setting goals, improving self-management and increasing awareness. Therefore, the use of health apps should be promoted while improving digital knowledge among users and developing data literacy. Another tool to support *adherence* can be the use of pictograms to describe recommendations. Elderly people with multimorbidity often use a schedule on which they mark the doses taken and place the sheets in visible places [31–33].

The consideration should be given to how to facilitate *adherence* to both the doctor and the patient. There is significant scope here for CSR activities by pharmaceutical companies.

SUMMARY

1. Compliance with therapeutic recommendations is an immensely important issue also in the case of chronic diseases.
2. Polish studies are needed to determine the extent of this phenomenon in relation to autoimmune diseases.
3. Research is needed to develop better strategies for working with the patient, in line with the idea that the patient should also play an active part in the therapeutic process.
4. It is appropriate to include clinical pharmacologists in the control and supervision of the pharmacotherapy process in relation to chronic diseases as well as post-transplant pharmacotherapy.

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