

The Patients' Compliance as an Essential Part of Successful Therapy Using the Example of Iron Deficiency Anemia

Khodjieva Gulirano Sayfullaevna

Assistant of the General Practitioners Advanced Training Department with Emergency Course,
Bukhara State Medical Institute named after Abu Ali Ibn Sino

Abstract: This article is devoted to pharmacoeconomics and patients' compliance to the therapy of iron deficiency anemia. These directions are relatively young in science and their importance often remains underestimated by most specialists. Pharmacoeconomics' main goal is to determine the most optimal medicine for treating the disease's cost-effectiveness ratio. Therefore, this review presents the main facts that determine the therapeutic efficacy of specific iron preparations and their clinical and economic analysis results. It also provides the statistical and theoretical substantiation of the significance of research and control of patients' compliance in the treatment of iron deficiency anemia.

Keywords: compliance; iron deficiency anemia; pharmacoeconomics; iron preparations.

Introduction. Iron deficiency is the most common form in the world of microelement deficiencies. Iron deficiency ranks first among the 38 most common human diseases, affecting more than 3 billion people on Earth [1,2]. This is the only form of micronutrient deficiency present in both developing and developed countries [3]. The clinically pronounced form of iron deficiency in the body is iron deficiency anemia (IDA).

IDA is a polyethyologic disease, the occurrence of which is associated with iron deficiency in the body due to violation of its intake, absorption or increased losses, characterized by microcytosis and hypochrome anemia [4]. Treatment of IDA with iron compounds (IC) is a complex and multifaceted field that requires knowledge of several nuances that must be taken into account when prescribing and monitoring therapy to achieve the optimal clinical effect.

Clinical efficacy of IC. Practice shows that the most common causes of ineffective treatment of IDA IC are the use of too low doses of the drug, short duration of therapy, impaired absorption, and treatment of chronic posthemorrhagic anemia without elimination of the source of blood loss [5]. Moreover, if the last two factors do not depend on the drug used, the rest are primarily determined by the drug's characteristics.

As a rule, the doctor chooses IC for the prescription to the patient, considering his own experience, information about the medicine, obtained at training cycles or exhibitions, from medical journals or the Internet, as well as material capabilities of the patient, that is, the possibility of purchasing the medicine for the entire course of treatment.

For many years, IDA therapy has included divalent iron drugs, mainly in iron sulfate. Iron sulfate preparations were considered the "gold standard" of IDA therapy, as they have the highest absorption capacity [6]. In this regard, it is no coincidence that most salt ICs have this very active substance on their basis. Gluconate, chloride and iron fumarate have a less pronounced ability to absorb [5,7].

However, the world experience in the treatment of IDA has shown that the use of divalent iron preparations in doses of 5-8 mg/kg of body weight per day leads to the development of side effects of IDA in the majority of patients, which may be the basis for drug withdrawal, dose reduction and treatment breaks [3,4]. In this connection, a trend to change IC with a divalent gland to less toxic IC with the trivalent gland has started to be observed in the world today [8]. The appearance of ICs based on the hydroxide polymaltose complex (HPC) has forced specialists to change the tactics and plan of IDA therapy.

Distinctive properties of IC with trivalent iron are high molecular weight, presence of trivalent iron hydroxide nucleus consisting of 260 atoms, high iron content in the nucleus (about 27%), and the presence of polymaltic shell instead of protein [7,8]. These characteristics make the iron in these preparations very similar in structure and valence to the natural iron compound molecule in the body - serum ferritin.

In general, randomized studies on the side effects of IDA treatment with IC (II) and IC (III) have shown their equal effectiveness in the less pronounced toxicity of the latter for the GIT [7,8,9].

Pharmacoeconomic issues in the treatment of IDA. A global health problem in most countries, regardless of their political and economic situation, is the need to continuously increase spending to provide health care to the population. This phenomenon has its peculiarities for the health care system in different countries. The main reasons for the cost increase in the health care system are socio-demographic, economic and medical factors [10].

One of the problems of domestic health care, which is the main prerequisite for the development of pharmacoeconomics, is generic drugs. The determining factor in this problem is precisely the cost and effectiveness of drugs. The economic factor is the leading one for the majority of the population. Among a wide range of drugs, including IC, the least affordable are original drugs, while their generics are cheaper because of the lower cost of their creation and clinical trials. However, manufacturers of these generics often extrapolate data on the original drugs' efficacy, which is not always justified [10,11].

Clinical and economic analyses are the solution to these problems because they are based on evidence-based medicine and comparative clinical trials. The data obtained with their help allows us to assess the importance of drugs for reasonable health care and determine the cost of additional benefits they possess [9,12].

First of all, the results of clinical and economic studies should be addressed to practicing doctors and their patients. In this case, the pharmaco-economic analysis data will allow choosing the optimal cost/efficiency ratio scheme of medication treatment, conduct treatment taking into account the quality of life of patients, reduce the length of stay in hospital and reduce the frequency of disability. All of this will lead to a decrease in all other costs, including non-material suffering and patients' psycho-emotional problems. [9,10,11].

IDA treatment is a significant clinical and economic problem, as IC treatment is long-term and numerous drugs are quite expensive. Besides, the treatment of severe IDA forms requires regular laboratory control to assess the dynamics, which also requires economic costs. Therefore, pharmacoeconomic analysis is of great interest [12].

If we consider the price of 1 package, 1 tablet, 1 ml of the preparation and 100 mg of IC most used by physicians in the treatment of IDA in Russia, then after assessing the amount of the active ingredient in these drugs, the attitude to the drugs themselves changes. If to recalculate for elemental iron, in IC (II), its content is several times less [7,9].

In particular, the comparison of IC Maltofer and Actiferrin in the form of droplets, specially designed for children of the first months of life, has shown that the iron content of 1 ml of Maltofer droplets is equal the iron content of 6 ml of Actiferrin droplets. The calculation of the drug price, in turn, showed that Maltofer is cheaper rather than Actiferrin. Similar calculations for tablet IC showed that 1 tablet of Maltofer equals 3 tablets of Phenulse or 3 capsules of Ferro-

Folgam. The IC price is higher: instead of two tablets per day, Maltofer has to use up to 6 tablets with constant monitoring of their intake, which is very inconvenient [9,12].

Pharmacoeconomic analysis results showed that it was more advantageous to use IC (III) for complete clinical and laboratory treatment of IDA. The higher cost of IC treatment (II) is the need for repeated treatment and an increase in the number of visits to the doctor due to the refusal of treatment or because of the side effects of taking IC [7,9,12].

The lower cost of using IC (III) is explained by the fact that their treatment leads to a positive result within the standard time frame, i.e., after 3-6 months after therapy. IC (II) may increase treatment time due to periodic drug withdrawal, more side effects and low tolerance. The results of the cost-benefit analysis of IDA treatment showed that the cost of treatment increases due to the consequences of discontinuing IC (II) [6,79].

Cost analysis showed that despite the high price of IC (III) packing, the cost of 100 mg of iron in all drugs is approximately comparable. Simultaneously, the cost of eliminating possible consequences, which can potentially appear in case of refusal from therapy, can be several times higher than the cost of used IC for the treatment of IDA [12].

Pharmacoeconomic analysis results show the necessity to use those ICs in the treatment of IDA, allowing the patient to get the best treatment. In this regard, doctors should be aware of the benefits of IC not only from a material point of view but also in terms of the quality of treatment, rapid improvement in the patient's quality of life, and the absence of complications. Doctors must be fully aware of the economic component of the issue and explain to patients the benefits of IDA treatment with specific ICs.

Patients' compliance for IC therapy. The study of patients' attitudes to the prescribed therapy and the degree of compliance is a relatively new scientific research area. This area's development is due to the doctor-patient interaction paradigm's significant role, the transition from the paternalistic model to the partnership, and the patient's awareness of their active role in therapy. Doctors must understand the actual situation from avoiding mistakes in the form of unreasonable prescription of large doses and intensification of therapy, leading to an overdose. Finally, the economic factor plays a significant role since significant damage to the health care economy can be caused by patients' neglect of prescriptions [13].

Compliance is the patient's precise fulfillment of all medical recommendations and prescriptions within the framework of prevention, treatment, and rehabilitation. WHO offers a more complex definition: "the extent to which the patient's behavior concerning the use of a drug, the implementation of recommendations on nutrition or lifestyle changes to the prescriptions and instructions of the doctor" [14].

According to WHO, 5 groups of factors causing noncompliance are identified: social and economical (a financial situation, low cultural level, old age), systemic (doctor-patient relations, education of paramedics, possibilities of the health care system, duration of medical consultation), related to the disease (degree of severity of symptoms, comorbidity, stage of disease progression, availability of effective therapy), caused by the therapy (complexity of the regime, duration of treatment, unwanted reactions to drugs, the ineffectiveness of the prescribed therapy), due to the patient's peculiarities (forgetfulness, knowledge about the disease, fear of unwanted side effects, premature termination of treatment). Along with the presented factors, one should not underestimate patients' distinct mental characteristics, often due to a system of their views and perceptions, including those established in a certain community and territory [13,15].

Insufficient compliance is a widespread phenomenon and a problem for health care systems in many countries. According to WHO, in developed countries, only 50% of patients with chronic diseases have long been in strict compliance with medical recommendations; in developing countries, the rate is even lower [14,15].

Even in a country like Germany, where there is a high level of commitment to society, patients' non-compliance is relevant. According to the ABDA (Federal Union of Pharmacy Associations), more than 50% of all prescription drugs are not taken following medical guidelines. In order to prevent non-compliance, in Germany, the implementation of medical prescriptions is monitored. A database on prescriptions has been created, which currently covers 80% of patients for whom drugs are paid by health insurance [13,14,15].

The direct consequence of non-compliance with the doctor's recommendations is the lack or insufficient effectiveness of treatment, deterioration of the patient's condition, development of complications, more frequent relapses, development of drug resistance, exacerbation of the underlying disease, adverse drug effects and increased risk of complications. All of the above affects the health of patients and causes significant damage to the health budget.

In the United States, losses due to non-compliance are estimated at \$100-300 billion annually. Over 5% of all hospitalizations in the country are due to inadequate compliance. In large European countries, additional losses due to non-compliance in patients are estimated at 10 billion euros annually. According to reports of the European Federation of Pharmaceutical Industry Associations, patient non-compensation costs the European governments' budget almost 125 billion euros and contributes to the premature death of about 200 thousand Europeans every year [15,16].

Thus, patient compliance research is a trend that is developing quite rapidly. Its results are interesting and significant for healthcare professionals of different profiles. The importance of patient compliance in the treatment of IDA is due to many factors. The main ones are the long duration of therapy, the high cost of IC, the prevalence of side effects of IC that cause pain to patients during therapy, and the underestimation by patients of the severity of the disease and its consequences. In this regard, the study of this aspect of IDA therapy is relevant for regions with a high prevalence of pathology, as it may contribute to the development of new methods of control over the treatment of patients.

Conclusion. Iron deficiency anemia is fully a non-contagious epidemic for modern society, which causes significant damage to the health of the most vulnerable groups in society, children and pregnant women. The high prevalence of iron deficiency anemia makes it necessary to re-evaluate its correction methods when patients' characteristics and the peculiarities of the attitude towards therapy in the whole population come to the fore. Analysis of the literature has shown that the issues of competent pharmacoconomics and strict compliance of patients to the therapy with iron preparations are an essential part of the treatment, determining in many cases, its positive outcome.

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