

Rheumatoid Arthritis: State of the Treatment Cost

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Abstract

Currently, there are three general classes of drugs commonly used in the treatment of rheumatoid arthritis: non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs): methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine, as well as biologic DMARDs (biologic agents - *genetically engineered* drugs): etanercept, infliximab, adalimumab, rituximab, certolizumab, anakinra, and other. Other immunomodulators are occasionally used including azathioprine and cyclosporine. Fortunately in the last few years, a shift in strategy toward the earlier institution of disease modifying drugs and the availability of new classes of medications have greatly improved the outcomes that can be expected by most patients. However, the high cost of modern technologies indicates a need to study the economic burden of rheumatoid arthritis for a rational choice of a particular method of treatment.

Keywords: *Rheumatoid arthritis; treatment, pharmaco-economical analysis.*

State of the Problem

The high social and economic importance of rheumatoid arthritis (RA), despite the relatively low prevalence, requires the implementation not only of effective and safe methods of treatment, but also of the economically less costly approaches to the treatment and rehabilitation of RA patients. Fortunately in the last few years, a shift in strategy toward the earlier institution of disease modifying drugs and the availability of new classes of medications have greatly improved the outcomes that can be expected by most patients [1-3]. It has been found that a disability in the previous 6 months is noted in 54% of RA patients, and in the previous 12 months in 66%. The average duration of temporary disability is 39 days per year. Studies have shown that the time from the RA onset to the disability varies widely from 4.5 to 22 years; the average is 13 years [4]. It is typical that the frequency of disability has an intermittent character during the first year after diagnosis of RA, and this parameter decreases linearly in the next 4-9 years. Timing of the disability onset differs greatly in different countries because of various factors, including the social policy. Early diagnosis and timely appointment of adequate pharmacotherapy largely determines the prognosis of RA. Most RA patients need expensive conservative treatment and more than a third of them need a total replacement arthroplasty [5]. In spite of the average cost of standard hospital care in Russia, which is about 250,000 RUB, the actual amount of funding does not exceed 20% of the required

amount [6]. Moreover, it is necessary to take into account the fact that patients are not adequately provided with subsidized medicines in the outpatient phase. According to E.L. Nasonov et al. [7], in general, the inpatient and outpatient treatment of RA patients, including subsidized medications, costs about 0.34–1.2 million RUB depending on the frequency of hospitalizations. A comparative study of the economic burden of RA, osteoarthritis (OA) and high blood pressure (HBP), according to researchers from Ontario [8], showed that the overall costs were CA\$9,300, CA\$5,700, and CA\$3,900 per year, respectively. Indirect costs related to RA were up to five times higher than indirect costs incurred by patients with OA or HBP, or both. The presence of comorbidities was associated with disease costs for all diagnoses, cancelling out potential effects of age or sex [8]. In addition, indirect costs for each RA patient were in 2–3 times higher than direct costs. Indirect costs included cash payments for adult patients and parents of sick children for sick leave, the costs associated with a decrease in the working-age population at the expense of adult patients who are forced to leave work before retirement age, and the costs for children with disabilities who annually join the ranks of disabled adults and are unable to work after reaching working age. According to the data in the literature, the number of days of disability among the working patients with rheumatic diseases was 1,116,534 or 2.3 per 100 employees [7]. The level of disability and the costs associated with lost productivity due to RA is the highest compared with other nosological forms. D. Huscher et al [9], studying data

from more than 7,000 outpatients with rheumatic diseases in Germany, determined the cost of the diseases: the direct costs were €4,737 for RA per year, €3,676 for ankylosing spondylitis, €3,156 for psoriatic arthritis, and €3,191 for systemic lupus erythematosus. The costs associated with disability reached €15,637, €13,513, €11,075, and €14,411, respectively. Increasing the duration of the disease and the deterioration of the functional state produced an increase in costs. Thus, the decrease of the functional state of RA to at least 50% of the norm was accompanied by the disability payments in the amount of €34,915 [9]. In addition, RA patients have also high loss of the home productivity. According to S. Verstappen et al [10], each patient with RA loses €2,045-3,882 each year during the first 3-4 years, the losses increase up to €4,434-9,957 per year in the next 3-4 years. J. Ruof et al [11], who performed retrospective analysis for the cost of RA on the basis of insurance payments for 338 RA outpatients, showed that the direct medical cost per year was an average of €3,815, of which 73.7% was for the ambulatory care and 24% for stationary care. In the structure of the cost for outpatient care, drug costs amounted to €1,019, the out-patient visits to €323, the cost of diagnostic and therapeutic procedures to about €185 and of various devices to €168 [11]. A study of the costs for RA patients in Germany showed that, on average, each patient spends about €417.2 their own funds per year. This represents about 15.3% of the total direct costs for RA treatment. In this case, the cost of medicines and medical consultations was €99 and €38.4, respectively. Thus, it is necessary to consider not only the documented costs of insurance companies, but also the personal costs to patients [12]. The results performed in Canada also showed that the treatment costs increase with every year [13].

Given that the cost of the RA treatment largely depends on the duration of the disease, S. Verstappen et al [14] studied the annual direct costs, depending on the disease duration. It was found that the annual direct costs amounted to an average of €523 for disease duration under 2 years, €3,930 for 2-6 years, €4,664 for 6-10 years, and €8,243 for more than 10 years. If the cost of treatment in the first 2 years was associated with the large number of diagnostic procedures and consultations, as well as careful selection of therapy, after 10 years of disease, about 40% of the costs consisted of the cost of assistive devices and the adaptation activities in connection with the violation of the functional state. It should be noted also that the seropositive RA is associated with a significant increase of costs for the later stages of the disease [14]. According to other authors, the direct costs for RA treatment with traditional DMARDs include up to 60% of the total cost for monitoring and treatment of side effects [7]. The above data underline the social and economic importance of RA and the necessity for a differentiated approach to the treatment of this disease.

In the US, before the wide clinical application of biologic agents, overall cost for the management of \$38.4 million RA patients was \$116.3 billion. In this case, the direct costs were \$51.1 billion, and indirect costs were \$65.2 million.

It is known that methotrexate (MTX) is now considered as the "gold standard" in rheumatology [15]. The high efficiency

of MTX as monotherapy or in combination with other drugs has been confirmed by numerous clinical studies [16]. The cost of treatment with methotrexate at a dose of 7.5-15 mg per week does not exceed of \$1,000 per year [6]. It is well known that monotherapy with DMARDs is effective in the initial stages of RA. As a rule, patients with RA seek treatment at the advanced stages of the disease, which require the use of combination therapy. This is primarily a combination of DMARD and other drugs, in particular, with biological agents. So, infliximab and etanercept and other biologics have been approved by the FDA to treat moderate to severe rheumatoid arthritis that has not responded to an adequate trial of one or more of the traditional disease modifying antirheumatic drugs (DMARDs). They are expensive (usually over \$12,000 per year in the US), generally effective, well tolerated and quite safe in most patients, but do increase the risk of infections. Their safety can be enhanced by proper screening procedures (e.g., TB skin test) and periodic monitoring of blood tests. Because of their expense and side effects, most people with mild to moderate rheumatoid arthritis are treated with MTX before a biologic agent is used unless they are unable to take methotrexate because of side effects or other conditions.

Biologic agents may be used alone, but are often given in conjunction with other DMARDs (e.g., methotrexate, leflunomide, hydroxychloroquine, sulfasalazine), to increase the benefit and limit potential side effects. Along with a large evidence base for the clinical efficacy of these drugs in the treatment of RA patients, the economic aspects of their application are still poorly understood in the CIS countries.

According to G. Kobelt et al [17], the efficacy of combination therapy with infliximab and MTX for 12 months in RA patients was superior to monotherapy with MTX, but in the next 10 years, this advantage was offset. However, the number of quality-adjusted life-years (QALY) in the second case becomes larger than that in the first case [17]. According to M. Suarez-Almazor et al [18], in view of the pharmacoeconomic effectiveness, the use of biologics that block TNF may be acceptable (<1000000\$/QALY) as a second-line therapy for RA, which is characterized as an inadequate response to therapy with other DMARDs.

A comparative study of the treatment costs for 1 year in patients with active RA (MTX+infliximab and MTX+adalimumab vs. MTX+placebo) showed that effectiveness of the therapy significantly increased with the application of these combinations compared to placebo+MTX. Depending on the criteria of efficiency (erosion score, joint space narrowing score and total score), costs amounted to \$4,506, \$23,048, and \$3,654 for infliximab and \$5,486, \$10,606, and \$3,616 for adalimumab, respectively [19]. At the same time it was found that the cost-effectiveness of infliximab and adalimumab for the total X-ray scores were comparable. The results of these studies suggest the equivalence of studied combinations, but the profitability of the drug use in clinical practice will depend on the actual doses. X. Gao et al [20], in assessing the profitability for the application of the TNF-inhibitors in conjunction with MTX (etanercept at 50mg/wk+MTX, infliximab at 3 mg/kg every 8 weeks+MTX, and adalimumab at 40 mg/2 weeks+ MTX) for one year in RA

patients, using the total radiological score as a measure of the treatment efficacy, has come to the conclusion that the combination of etanercept and MTX therapy was dominant, as evidenced by lower costs: €15,962 against €21,921 and €16,360, respectively, and higher efficiency: 80% vs. 59% and 72%, respectively. In this case, the dominant position of etanercept+MTX is saved, even if its price increases by 20% or effectiveness is reduced by 20% [20]. N. Bansback et al [21], using a mathematical model, studied the effect of adalimumab on the quality of life of 10,000 hypothetical patients with moderate to severe RA and showed that the use of adalimumab+MTX would lead to an increase in QALY ranging from 2.1 to 2.3, and the combination of etanercept and MTX therapy would give a comparable effect, but the results of the combination of infliximab and MTX therapy were comparatively worse. Application of the first two drug regimens was economically feasible for countries with a range of costs €35,000 to €42,000/QALY, and the infliximab administration is somewhat less favorable [21].

Assessment of the cost-effectiveness of treatment with etanercept and MTX in a 2-year TEMPO study with 682 patients with active RA, in view of the functional status, quality of life (Health Assessment Questionnaire Disability Index -HAQ), and disease activity, showed that disease activity has the significant influence on cost-effectiveness. In this case, the addition of etanercept to MTX for 2 years resulted in an increase in the cost up to €14,221 and an increase in QALY by 0.38. Ten years later, costs have increased by €42,148 and QALY increased by 0.91 [22]. K. Lee et al [23] analyzed 422 medical records of patients with disease duration of 11.8 years on average to determine the size and structure of the treatment cost of RA. The results of this analysis showed that the total annual cost amounted to €45,312, of which €41,486 was indirect costs and €3,826 was direct costs. At the same time, the indirect costs were mainly due to an increase in disability and the need for nursing assistance. There was a correlation between the total and direct costs and decline in functional status. N. Engel-Nitz et al [24] showed the effect of dose correction of TNF-inhibitors on the total cost. The increase in the doses of etanercept in 3.2% of RA patients, adalimumab in 12.5% and infliximab in 51% of RA patients has contributed to an increase in the direct costs per year up to \$2,448, \$13,373 \$18,019, respectively.

In the economic analysis of the costs, the place of the treatment (inpatient or outpatient) plays an important role. A study conducted in France showed that the cost of 31,706 hospitalizations due to RA amounted to €77,738,118 [25]. In the structure of total expenditure, a share of the costs for anti-TNF medications reached 24%. The direct costs for hospitalization were averaged to €1,853, and on anti-TNF medications to €660. In the structure of the total cost, the share of the cost for inpatient care was 86% [25]. According to W. Vanden Hout et al. [26], the costs for outpatient management of patients were lower than for inpatient treatment. S. Merkesdal et al [22] analyzed the cost of treatment and the costs associated with reduced productivity in ambulatory RA patients in 1998 and 2001. The results showed a reduction in costs in 2001 compared to 1998 from €5,570 to €355 with comparable

demographic and clinical indicators. Furthermore, in the cost structure, pharmacotherapy costs increased (from 9 to 26%, respectively) and the cost of hospitalization decreased (from 22% to 15%, respectively), and there was also a tendency to reduce the indirect costs (from 47% to 40%, respectively). Consequently, the use of expensive drugs for outpatient RA treatment is associated with a reduction of the economic burden of the disease.

Conclusion

Thus, the analysis of the literature indicates the paucity of research in the direction of the pharmacoeconomic efficacy of drugs used in RA treatment. It should be noted the range of drugs for treatment of RA that are included in this analysis is limited. No data for many DMARDs, as well as for other drugs except TNF-inhibitors and other biologics are included. Available data from the literature are characterized by a fairly pronounced scatter in results of pharmacoeconomic studies in different countries, and differences in methodological approaches to their implementation. Differences in funding, the effectiveness of economic development, the development of health insurance and medical aid organization does not allow for extrapolation of the results of Western studies to the national practice that requires modern pharmacoeconomic studies in Uzbekistan.

Competing interests

The authors declare that they have no competing interests.

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