MANAGEMENT OF RHEUMATOID ARTHRITIS PATIENTS IN ROMANIA

INTRODUCTION
Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, with unknown aetiology and an autoimmune pathogeny, characterized by a deforming and invalidating evolution arthropathy and multiple systemic manifestations. Worldwide, disease incidence is approximately 0.5/1000 for women and 0.2/1000 for men, and prevalence is approximately 1.7% for women and 0.7% for men. Medium age of disease onset is between 30 and 50 years but it can affect people at any age [1, 2, 3].

For our country geographic particularity, it is appreciated that rheumatoid arthritis affects around 1% from general population, so the total number of suffering people are estimated to be up to 180,000 [1, 4].

Risk factors for disease onset are: female gender, infectious agents, autoimmunity, genetic factors and not least, medium factors (smoking, alcohol consumption [1, 5, 6, 7]).

Rheumatoid arthritis has a preclinical debut up to 10 years, preceding clinic symptomatology. Once triggered, the natural course of the disease is early RA, established RA and late RA.

Early RA is dominated especially by pain and articular swelling, in the second stage (established RA) stiffness, articular deformity and fatigue are between implicated factors that make the patient unable to be independent (activities such as walking, dressing, cooking are practically impossible), culminates with disability in the late stage. Most often, the persons with established RA have to retire on early ages, which have a major negative impact on his/heir’s family but on the society too.

Although the perception is often that RA is a joint disease, in reality, it has a much broader impact on a person and it can affect a number of vital organs. The disease severity results also of percentages of patients that have to stop working in the first 5 years of the disease, 50%, and of percentages of patients with serious disability in the first two years of evolution, 10%, that has been shown in the epidemiological studies.

Over the time, more articles has been written about the epidemiology and RA societal impact, Kvien (2004) has concluded that RA can cause premature death (5 to 10 years life shortening) through an increased risk of cardiovascular disease, such as heart attack and stroke, genitourinary, gastrointestinal and respiratory diseases [8,9]. Pincus (1984) shows that patients with RA has a much lower quality of life then patients with migraines, blood hypertension, chronic obstructive pulmonary disease and diabetes [10]. So it results, that rheumatoid arthritis represents not only a medical issue, but a societal one, of public health problem [11].

Through its individual and societal consequences, rheumatoid arthritis has significant total costs, costs that are growing by the delays in diagnosis and therapy initiation or by the inefficient therapy management.

Key words: patient management, rheumatoid arthritis, efficacy, effectiveness therapeutic protocols, quality of life.

INTRODUCTION
Rheumatoid Arthritis is a chronic disease with long evolution which produces important consequences at the level of patient and society, a disease with several available therapeutic options, but not all of them having the same effects. The therapeutic measures are applied on a long term basis and they are, in most of the time, the result of medical practice guidelines developed at local or international level.

Methods
The authors made a revision of the local and international speciality literature regarding rheumatoid arthritis and studied the legal framework in Romania regarding the medical practice guidelines, therapeutic protocols and treatment reimbursement conditions.

Results
In Romania the management of patient with rheumatoid arthritis is based on several clinical and administrative decisions, reflected into the medical practice guidelines and therapeutic protocols with normative value. Because of high costs, the availability of biologic therapies for the rheumatoid arthritis patients is restricted only to these patients with approved treatment by the public payer, according to specific therapeutic protocols developed by the Ministry of Health and National Health Insurance House. The limited available financial resources in the social health insurance system create the conditions for waiting lists of the patients with medical recommendation for expensive therapies.

Conclusions
The management of patient with rheumatoid arthritis is a complex process related with patient factors, but also with the health system functionality. In Romania, the usage of newly and expensive treatments requires the utilization of some medical practice guidelines and therapeutic protocols which should rely more and more on the effectiveness rather than the efficacy of treatments, considering the fact that clinical data regarding effectiveness of drugs treatments started to be available.

Key words: patient management, rheumatoid arthritis, efficacy, effectiveness therapeutic protocols, quality of life.

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I. INTRODUCTION

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Although the perception is often that RA is a joint disease, in reality, it has a much broader impact on a person and it can affect a number of vital organs. The disease severity results also of percentages of patients that have to stop working in the first 5 years of the disease, 50%, and of percentages of patients with serious disability in the first two years of evolution, 10%, that has been shown in the epidemiological studies.

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Through its individual and societal consequences, rheumatoid arthritis has significant total costs, costs that are growing by the delays in diagnosis and therapy initiation or by the inefficient therapy management.

Key words: patient management, rheumatoid arthritis, efficacy, effectiveness therapeutic protocols, quality of life.
RESULTS

Results for objective 1.

Studying speciality literature regarding RA patient highlights that despite the fact that RA is a chronic illness with no cure, it exists the possibility to keep it under control and to reduce its consequences.

RA’s patient management should be guided by two major principles:

- Earlier and accurate RA diagnoses. This is essential for optimizing results and it is possible through a partnership between primary care health network and rheumatologist and, not least, by the education of general population for increasing addressability to a physician.

- Once RA diagnosis is established, it must take into consideration that therapy management is a complex one and it aims at optimization of long term quality of patient’s life through control of symptoms, structural damages prevention and normalization of functional and social activities.

At the time being, in the world and in our country too, there are delays in starting DMARDs up to 2 years, due to patient’s late presentation at a general practitioner or due to late referral at a rheumatologist [12]. This delay can do nothing but worsening the disease stage lowering the quality of life’s patient and in terms of society impact, nothing but increasing both direct and indirect costs [10].

EULAR (European League Against Rheumatic Diseases) and ACR (American College of Rheumatology) Committees recommends starting “Disease Modifying Anti Rheumatic Drugs” (DMARD) as soon as possible from the disease onset, ideally in the first three months, for the long term benefits on the structural joint damages. It has been proved that structural damages are greater in the first year versus the second and the third year, and up to 93% of patients have visible erosions on radiographic images in the first 3 years from onset [13,14].

The clearly established target in RA patient’s therapy is to permanently keep the disease under control, meaning in remission, or to keep it in low disease activity (for the most severe cases) [15].

The international consensus regarding the accurate treatment of a patient with RA, presume 4 major steps:

1. Starting DMARD therapy as soon as possible from the clinic onset of RA, ideally in the first 3 months.

METHODOLOGY

For realizing the proposed objective, the authors used the following:

- Reviewing the RA’s specialized literature worldwide and in Romania,
- Studying regulatory framework in Romanian legislation regarding guidelines of medical practices, disease therapeutic protocols and RA patient’s treatment reimbursement within the social health insurance system.

Specific objectives were:

- Revision of RA speciality literature for a better understanding of RA patient management particularities and for seeing consensus points and variable treatment aspects regarding RA patient.
- Critical analysis of Romanian legislative framework for medical practices guidelines, therapeutic protocols and NHIH (National Health Insurance House) reimbursement for RA patient therapy’s costs.
Current therapy algorithm, provided by the majority of therapy guidelines, is: starting Methotrexate (a DMARD therapy), followed by increasing dose, or addition of another DMARD once insufficient response appears, the so-called “step-up strategy”. If remission is not obtained after 2 cures of 12 weeks each, the treatment passes on the next step, starting a first line biologic therapy [16].

2. Tight control of disease activity at 3, maximum 6 months in order to suppress flares by adjusting or changing therapy until the final target is achieved: remission or low disease activity status.

Evaluating therapy results is made by the analysis of acute phase reactants (C reactive protein - CRP and erythrocytes sedimentation rate - ESR) and by calculating composite indexes which measure the disease activity: DAS28 (the calculation is made through a standard formula with: swollen and tender joints number, one of the acute phase reactants and patient global health), delta DAS (the difference of starting DAS28 and final DAS28), EULAR response (good, moderate and low response), ACR 20, 50, 70 response etc.

3. Initiating biologic therapy when not effective response to conventional DMARDs has installed, with the same monitoring recommendation. According to actual medical practice guidelines, biologic therapy is initiated with drugs from anti-TNFα therapeutic class (infliximab, etanercept, adalimumab, golimumab or certolizumab pegol) or anti IL-6 therapeutic class (tocilizumab).

Choosing between one anti-TNFα or anti IL-6 therapeutic drug is at physician’s level, according to his clinical experience and/or at patient’s desire, because there are no “head to head” clinical studies to prove that one drug is more effective than other. In the same time, the response at anti-TNFα therapeutic class is achieved only for 40% or so of patients [17, 18].

4. Continuing biologic therapy, with others therapy schemes, when the patient is not responding or is an insufficient responder to first biologic agent. In this situation, the available therapeutic options are:
   - Changing therapeutic class with anti CD 20 (rituximab) or anti T lymphocytes agent (abatacept),
   - Changing the drug in the same class anti-TNFα,
   - Keeping the same anti-TNFα, increasing the dose.

As we mentioned there is a consensus regarding this 4 steps of RA patient therapy scheme and the medical practice guidelines are, in general, the same in Romania as worldwide. Actually, the only step where there are more treatment options (and are different recommendations in practice guidelines from different countries) is the step 4.

In the step 4 of treatment, there are differences in therapy protocols in different countries, according to allocated financial resources, available drugs on the market, etc.

This therapy protocols from different countries have either regulative value (Great Britain, Norway, Finland), either recommendation value, being the most frequently found in medical practice from those countries. So, in Great Britain, NICE (National Institute for Clinical Excellence) issued mandatory guidelines for public health system that says „Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of, other disease-modifying anti-rheumatic drugs (DMARDs), including at least one tumour necrosis factor (TNF) inhibitor. Adalimumab, etanercept, infliximab and abatacept, each in combination with methotrexate, are recommended as treatment options only for adults with severe active rheumatoid arthritis who have had an inadequate response to, or have an intolerance of, other DMARDs, including at least one TNF inhibitor, and who cannot receive rituximab therapy because they have a contraindication to rituximab, or when rituximab is withdrawn because of an adverse event” [19].

In Norway and Finland there are therapy guidelines which says that „rituximab in combination with methotrexate is recommended for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to, or are intolerant of one anti-TNFα, with the exception of rituximab intolerant or contraindication”.

Other countries from Western Europe developed cost-effectiveness studies with the objective of increasing patient’s access to treatment. So, in Spain, Alvarez (2006) concluded that „rituximab, for all patients with inadequate response to anti-TNFα is a therapeutic option which brings a significant incremental cost gain per Quality Adjusted Life Year (QALY) under already accepted therapies. Annual costs of RA therapy in Spain are reduced by using rituximab, which, in addition, reduce the lifelong treatment costs when prescribed as alternative to one anti-TNFα” [20]. In Germany, Schach (2006) has reached the conclusion that “rituximab, for patients with inadequate response to anti-TNFα, is a therapeutic option which brings a significant incremental cost gain per QALY under already accepted treatments. In conclusion, rituximab offers the chance of reducing the lifelong cost’s treatments when is used as an alternative to anti-TNFα” [21]. In Italy a Giuliani study (2006) concluded that “rituximab brings a favourable cost efficacy ratio per QALY gained at patients with inadequate response to anti-TNFα, from Italian health system perspective. Rituximab offers the possibility of treating more RA patient’s within the same allocated budget or it the possibility of reducing total costs of RA treatment” [22].

In Romania, the only specialty study, founded by authors, conducted in this direction, was realized and published by Ancuta I, Codreanu C, Ionescu R, Bolosiu H, Parvu M, Georgescu L (2010).
This observational study, based on the analysis of NHIH approved patients, with biological treatment, concludes: “cycling between anti-TNFα therapeutic drugs after failure at the first anti-TNFα has no benefits for patients, because DAS28 increased after the second stage of the treatment. Incomplete immunosuppression of the first anti-TNFα may induce significant treatment resistance in the second stage. Introducing rituximab after the first anti-TNFα failure has proved to be a more efficacious option, by realizing the accumulation of clinical benefits and sustained response by lowering DAS28 with every rituximab cycle. This strategy is also more efficient, by lowering the cost per DAS28 point, in comparison with rituximab administered after the second anti-TNFα failure. Because of the above, cost-benefit ratio is clearly in favour of starting rituximab treatment immediately after the first anti-TNFα failure, which is also our recommendation to NHIH” [23].

**Results for objective 2.**

In Romania, the legal framework covering the management of patient with rheumatoid arthritis (RA) could be separated in three major areas:

**A. Medical practice guidelines.**

These guidelines are developed by the Speciality Consultative Commissions of the Ministry of Health (MoH), and formalized through a ministerial order. These guidelines include the general framework for diagnosis and treatment for different diseases, including RA. The guideline for RA was developed in year 2010 and represents the Annex 1 of the MoH order no. 1322/2010, published in Romanian Official Gazette no. 784bis from 24.11.2010.

According with this guideline, the treatment options in Romania are the same with the 4 options presented above, the guideline being in line with EULAR and ACR recommendations.

The specific aspect of this Romanian guideline resides in the fact that the guideline is merely a wish than a model to be currently used in medical practice. According with the guideline, the therapy with biologic agents could be based on several agents (infliximab, adalimumab, etanercept, golimumab, certolizumab pegol, tocilizumab and abatacept). From these agents golimumab, certolizumab pegol, tocilizumab and abatacept are not reimbursed by the social health insurance system (N.R. at the time of publishing the article – June 2011), which means that the access of patients is limited to only several biologic agents, even the guidelines recommends also other medication.

**B. Therapeutic protocols covering drug prescription.**

The therapeutic protocols covering prescription of public reimbursed drug within the social health insurance system are approved by a common order issued by the minister of health and the president of NHIH, and target only the drugs approved to be used in the social health insurance system.

The last therapeutic protocols for patients with RA was approved also in 2010 (MoH/NHIH common order no. 461/477/2010, published in Romanian Official Gazette no. 386bis from 10.06.2010). The protocol presents the following 4 steps for the treatment (almost the same with the steps from the medical practice guidelines, but restricted to the drugs reimbursed in the social health insurance system):

1. Starting the conventional therapy with DMARD drugs;
2. Disease monitoring every 3 (maximum 6) months;
3. Starting the biologic therapy (when the DMARD drugs lose their effectiveness) with agents from the class anti-TNFα (infliximab, etanercept, adalimumab);
4. Continuing the biologic therapy, when the first anti-TNFα drug is not any more effective, with one of the following options:
   - Changing the class through the introduction of a therapy with an anti CD 20 (rituximab) agent;
   - Changing the anti-TNFα drug and moving to another drug from the same class (anti-TNFα);
   - Keeping the same anti-TNFα drug, but increasing the doses.

The protocol presents situations when the medical practice guidelines recommend some therapeutic options, not available because the respective drugs are not yet approved for reimbursement in the public system. Probably, after the update of the public reimbursement drugs list (the last revision being done in 2009) the therapeutic protocols will be revised to reflect the new therapeutic options recommended in the medical practice guidelines.

**C. NHIH reimbursement of the treatment for RA patients.**

For the treatment of RA using the drugs from DMARD class there are not specific rules, it is necessary only a prescription from a rheumatologist. For access at a biologic therapy (steps 3 and 4 from the below presented model) it is required an individual approval released by the NHIH, through the RA Expert Commission. For these patients, the reimbursement steps are:

- The rheumatologist prepares the medical file on a paper, which includes the following information: patient personal data, the consent of the patient for therapy, the diagnostics, comorbidities, the previous therapy and the patient evolution. The file includes also the physician request for a specific biologic agent (according with the therapeutic protocol).
• The medical file is sent towards the local health insurance house which collects them and, based on available fund, send them towards the RA Expert Commission from the NHIH.
• At national level (NHIH) the RA Expert Commission approves or not every medical file, based on therapeutic protocols and available resources. The approval is required every 6 months, for new or continuation of biologic therapy.

Once the biologic therapy approved, the patient could get the treatment for maximum 6 months, then it is done an evaluation of the treatment effectiveness and consequently a decision is taken regarding the next therapy. The limited resources available at the NHIH level produce some unfortunate situations when a patient receive the biologic therapy with benefits on the disease, but with discontinuity on administration (based on requirement of approval every 6 months). In this situation, the clinical benefits already cumulated start to decrease, the patient disease brings more disability and the patient should restart the therapy from the step when it was temporarily stopped.

In this context, the head of NHIH, preoccupied by bringing a major improvement in Romanian health insurance system and in quality of medical and pharmaceutical care, has implemented the Unique Integrated Informatics System (SIUI) of the social health insurance system. SIUI is a key factor in developing and improving the management of unique national health insurance funds and for offering quality medical and pharmaceutical care.

SIUI has a 3 level hierarchical structure, represented by NHIH, Local Health Insurance Houses (LHIH) and medical and pharmaceutical care’s providers, his major functions being: the management of unique national health insurance funds, the management of insured people, transparent medical and pharmaceutical care suppliers, transparent paying contributions, ensuring the quality control of medical and pharmaceutical care.

Through the implementation of SIUI, NHIH will benefit from:
• National Data Bases, with all the data and information necessary to rigorous evidence at the whole system, permitting the unique identification of every single insured person and RA patient, one of the essential conditions for reducing the system errors;
• The efficiency of health insurance system by national uniformity in applying rules, taking over the reports from suppliers and LHIH to NHIH;
• More efficient allocation of the health insurance system budget.

DISCUSSIONS

The introduction of the therapy with biologic agents dramatically improved the RA treatment and changed the therapeutic objectives of the disease. Because the costs of these drugs are high, the increase of their usage means new resources and a burden for society. The analysis done proves the need for special attention on updating the guidelines and protocols and for the establishment of some costing criteria when decisions are taken regarding the management of patient with RA.

Meantime, there are some local specific Romanian conditions which produce particularities of the management of RA patients. The most important specific conditions are:
• The lack of education at the population level regarding these disease, which leads to late establishment of diagnostic and a low addressability towards the health care system during the first phases of the disease;
• The lack of education of the primary care physicians regarding the precious diagnostic or the referral of these RA patients towards rheumatologists from the first signs and symptoms of disease;
• The presence of some differences between the medical practice guidelines and the therapeutic protocols, because of the lack of update for public reimbursement drugs list produce a barrier to access at new drugs for the patients (last update of the list was done in 2009);
• The presence of the waiting lists for access to biologic agents, because of the limited resources available. Because of these waiting lists, some patients wait more than ½ year for the beginning or continuation of the therapy (with losing of the clinical benefits cumulated by that time). This aspect is both in patient expense (because of the joint lesions advancement) and society expense (because of the increased costs to regain the lost clinical benefits);
• The lack of a RA national patient register leads to increased incapacity of efficient management of limited financial resources.

Other social and economic aspects which worth to be mention (without presenting them in extenso) is:
• The lack of rheumatologists in some districts;
• The heterogeneity of providers of clinical care for patients who require biologic agents;
• The temporarily lack of some drugs from the pharmacies etc.
CONCLUSIONS

The management of patient with rheumatoid arthritis is a complex process related with patient factors, but also with the health system functionality (the moment of diagnostic, access to health care services, comorbidities etc.). In Romania, the usage of newly and expensive treatments requires the utilization of some medical practice guidelines and therapeutic protocols which should rely more and more on the effectiveness rather than the efficacy of treatments, considering the fact that clinical data regarding effectiveness of drugs treatments started to be available.

The management of the RA patient is done in Romania at a level comparable with other European countries, but there are some local limitations which restrict the achievement of a performing management at the level of all RA patients.

In Romania, the accomplishment of a better management of RA patients and an increased efficiency of health care resources utilisation could be done through the implementation of some key measures: the development of a RA national register, the clarification of the RA patient route within the health system, the better collection of the patient clinical data, an improved communication between NHIH, physicians and pharma industry, the continuous update of drugs list and therapeutic protocols and the development of local clinical effectiveness and cost-effectiveness studies.

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