ORIGINAL ARTICLE

PARTICULARITIES OF TREATMENT WITH CONVENTIONAL SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDs) IN A GROUP OF PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Rheumatoid arthritis (RA) is a systemic inflammatory disease with destructive joint damage, causing severe functional impairment. Due to the complex mechanism of action of the various representatives from the group of conventional synthetic (CS) DMARDs, the different side-effect profile and the variability in patient response to treatment, the therapeutic management of RA with CS DMARDs is a real challenge in everyday clinical practice. The present study aims to identify the specific features of treatment with conventional agents in a group of RA patients monitored in an outpatient clinic. The present study was an observational, retrospective, descriptive cohort type of study, in witch, we included patients diagnosed with RA under treatment only with CS DMARDs (30 patients). Demographic, clinical and treatment data were registered and also adverse reactions to treatment. Effectiveness of treatment was evaluated using disease activity score for RA (DAS28). All data presented are expressed as mean ± SD for continuous variables and as number and/or percentage for categorical variables. The analysis of the treatment plan showed that methotrexate (MTX) was the most frequently prescribed conventional drug as first line therapy in 26 (87%) of the patients, in monotherapy. It was registered that only 5 (17%) of the analysed patients received CS DMARD in monotherapy and 25 (83%) in combination therapy. In our study group, the recommended treatment was considered effective in 53% of cases. One in three patients experienced adverse reactions to therapy. The most common adverse reactions were muco-cutaneous, followed by respiratory and digestive ones. The most prescribed CS DMARDs was MTX and the most used therapeutic strategy was step-up combination therapy. The initial treatment plan ensured the effective control of the disease in about half of RA patients. The adverse reactions of CS DMARDs agents were not of vital importance.

Rezumat

Artrita reumatoidă (AR) este o boală inflamatorie sistemică care determină destrucție articulară ireversibilă, cauzând insuficiență funcțională severă. Datorită mecanismului complex de acțiune ai diverșilor reprezentanți din grupul antireumatice modificatoare ale bolii (MAMB) sintetice convenționale (SC), al profilului diferit de reacții adverse și a variabilității răspunsului pacientului la tratament, managementul AR cu medicamente MAMB SC este o adevărată provocare în practica clinică de zi cu zi. Studiul de față își propune să identifice trăsăturile specifice ale tratamentului cu agenți convenționali într-un grup de pacienți cu AR monitorizați în ambulatoriul de specialitate. Studiu de față este tip cohortă, retrospectiv, descriptiv, observațional, în care, au fost incluși pacienți diagnosticați cu AR în tratament numai cu MAMB SC (30 pacienți). Au fost înregistrate datele demografice, clinice și de tratament care au inclus de asemenea, reacțiile adverse la tratament. Eficacitatea tratamentului a fost evaluată cu ajutorul scorului activității bolii pentru AR (DAS28). Toate datele prezentate sunt exprimate ca medie ± DS pentru variabile continue și ca număr și/sau procentual pentru variabile calitative. Analiza planului de tratament a arătat că metotrexatul (MTX) a fost agentul convențional prescris cel mai frecvent ca primă linie de tratament la 26 (87%) dintre pacienți, în monoterapie. Doar 5 (17%) dintre pacienții analizați au primit MAMB SC în monoterapie în timp ce majoritatea pacienților (83%) au primit terapie combinată. În lotul nostru de studiu, tratamentul recomandat a fost considerat eficient în aproximativ jumătate din cazuri (53%). Unul din trei pacienți au prezentat reacții adverse la terapie. Cele mai frecvente reacții adverse au fost muco-cutanate, urmate de reacții la nivelul tractului respirator și digestiv. Cel mai prescris MAMB SC a fost MTX iar strategia terapeutică cea mai utilizată a fost terapia combinată de tip *step-up*. Planul de tratament inițial a asigurat controlul eficient al bolii în aproximativ jumătate dintre pacienții cu AR. Reacțiile adverse ale agenților MAMB SC nu au fost de o importanță vitală.

Keywords: rheumatoid arthritis, DMARDs, adverse reactions, therapeutic strategy

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease with chronic evolution, with destructive bilateral and symmetrical joint damage, causing functional impairment. RA is a major cause of morbidity, mortality, disability and handicap. It is the most common inflammatory rheumatic disease, reaching a prevalence of 1% in the general population, predominantly affecting females (F:M = 3:1) with a peak in disease incidence between 35 and 50 years of age. The incidence is higher in northern Europe and America than in southern Europe or Africa [16].

Due to its severe progression towards irreversible joint damage, as well as the presence of systemic manifestations, it becomes clear that it is important to quickly establish an effective therapy in newly diagnosed patients. The more detailed became the understanding of the pathophysiology of the disease the more it enabled the development of targeted therapies such as the disease-modifying anti-rheumatic drugs (DMARDs) [6]. According to recent European League Against Rheumatism (EULAR) [22] recommendations, they are classified into: conventional synthetic DMARDs (eg. leflunomide (LEF), methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HQ), cyclophosphamide, azathioprine), targeted synthetic DMARDs (tofacitinib, apremilast), biological and biosimilar DMARDs (anti TNF-alpha, anti-CD20, anti-IL6, anti CTLA4). Corticosteroids are considered to be a symptomatic medication, being administered for short periods of time in low doses (up to 15 mg/daily prednisone or equivalent). Other therapeutic approaches include interdisciplinary disease therapy: physiotherapy, occupational therapy, orthopaedic physical therapy, psychological and nutritional counselling [1, 3, 9].

The purpose of RA treatment is to achieve remission. Remission is defined as the absence of inflammatory syndrome, of inflammatory joint pain, of morning stiffness and asthenia and no radiographic progression evaluated on consecutive radiographs [3]. If this is not possible, the target is to slow the progression of the disease by maintaining a low score of disease activity, which relieves the symptoms, maintains joint function and ensures good quality of life.

Although biological DMARDs act specifically on key elements of the pathogenic chain of the disease, the severity of their potential side effects, the high cost and the short duration of observation in clinical practice limit their use [6]. Therefore, conventional synthetic (CS) DMARDs are the first treatment option in the management of RA.

Due to the complex mechanism of action of the various representatives from the group of CS DMARDs, the different side-effect profile and the variability in patient response to treatment, the therapeutic management of RA with CS DMARDs is a real challenge in everyday clinical practice.

The present study aims to identify the specific features of treatment with conventional agents in a group of RA patients monitored in an outpatient clinic.

Materials and Methods

This was an observational, retrospective, descriptive cohort type of study. The study included patients who were diagnosed with RA according to the American College of Rheumatology (ACR)/EULAR [2] criteria, at the Department of Rheumatology of the Clinical Hospital for Infectious Diseases in Cluj-Napoca, Romania, from January 2011 until February 2015. Longitudinal data were collected retrospectively from patient observation charts corresponding to January 2011 - February 2015. Evaluation visits were established every 4 months, unless the activity of the disease required a more frequent follow-up. In his study, we included patients diagnosed with RA under treatment only with CS DMARDs. Patients with RA under treatment with biological DMARDs, patients with undifferentiated arthritis and other rheumatic disease (psoriatic arthritis, microcrystalline arthritis, reactive arthritis) were excluded.

An individual record was compiled for each patient and the following parameters were registered: demographics, age at onset, disease duration since diagnosis, the number of tender joints, the number of swollen joints, radiographic grade of the disease according to Steinbrocker`s criteria (stage 1 - 4) [24], the treatment administered (type, dose and route of administration of CS DMARDs), duration of treatment with a particular type of CS DMARD, the number of DMARDs administered, the use of monotherapy or combination therapy with DMARDs, adverse reactions to treatment, erythrocyte sedimentation rate (ESR) level (1 h, normal value < 2 mm/h) C-reactive protein (CRP) level (normal value < 0.5 mg/dL) the presence of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies, associated comorbidities.

Effectiveness of treatment was evaluated using disease activity score for RA (DAS28) [19]. A DAS28 above 5.1 means high disease activity whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6. If low disease activity was not achieved, patients were monitored every 3 months. Patients with high disease activity were monitored monthly.

All data presented in the Figure and Tables are expressed as mean ± SD for continuous variables and as number and/or percentage for categorical variables.

Microsoft Office - Excel 2007 was used for statistical analysis.

The study was conducted according to guidelines for good clinical practice. All participants gave written informed consent and underwent a comprehensive medical history, physical examination, and laboratory tests. The working protocol was approved by the local ethic committee according to the Helsinki Declaration.

Results and Discussion

The results of demographic data analysis in the study group are presented in Table I.

Table I

Patient group - baseline values

Number of patients	30
Age (years)	60.2 ± 14.17
Women	21 (70%)
Average disease duration (years)	3.4 ± 1.1
Patients with elevated ESR levels (1 h)	19 (63%)
Patients with elevated CRP levels (mg/dL)	4 (13%)
Number of tender joints (NTJ)	8.4 ± 7.2
Number of swollen joints (NSJ)	4.8 ± 3.4

In the group of patients included in our study, 23 (77%) had positive RF and 14 (47%) had positive anti-CCP antibody levels, but anti-CCP antibody levels were determined only in 17 (57%) of the patients in the study. At baseline, 4 (13%) of the patients included in the study showed elevated CRP levels and 19 (63%) had elevated ESR levels. Most of the patients included in this analysis 13 (43%) had radiographic stage II, 11 (37%) stage I, 5 (17%) stage III and 1 (3%) stage IV radiographic RA. The most frequent comorbidities in our study group were cardiovascular diseases.

The analysis of the treatment plan showed that MTX was the most frequently prescribed conventional drug as first line therapy in 26 (87%) of the patients, in monotherapy. Twelve (40%) of the patients received therapy with MTX between 3 and 11 months, and 7 (23%) between 12 and 19 months. The rest of the patients 7 (23%) were treated with MTX for more than 20 months. The most frequently administered dose of MTX assessed at the last visit of each patient was 20 mg/week (40% of patients). The most common route of administration of MTX was oral administration in 22 (73%) of the patients.

Twenty-two patients (73%) in our study were treated with hydroxychloroquine (HQ). We found that in most of the patients, 12 (40%) the duration of HQ therapy was between 3 and 13 months, which approximately coincided with the duration of treatment with MTX. Almost half of the patients, 13 (43%) received 400 mg HQ/day, 9 patients (30%) 200 mg HQ/day and 8 (27%) had no HQ treatment. Out of the 22 patients treated with HQ, 15 (68%) patients were concomitantly treated with MTX. The rest of 7 (32%) patients received HQ in combination with LEF. LEF was prescribed mostly as a second line treatment in a dose of 20 mg/day. Thus, 16 patients (53%) received treatment with LEF as second line treatment. LEF was prescribed as first line conventional agent in monotherapy only in 4 (13%) patients. Eleven patients (36%) in the study were treated with SSZ as step-up second line treatment, most of them with a dose of 2 g per day. In these patients, SSZ was used in combination therapy either associated with MTX in 4 (36.4%) patients or with LEF in 7 (63.6%) patients.

At the end of the evaluation period it was registered that only 5 (17%) of the analysed patients received CS DMARD monotherapy. Most of the patients, 25 (83%) received combination therapy with two agents. Only a small percentage of patients had at some point during the study period triple combination therapy (3 (10%)).

In sixteen (53%) of the cases the value of DAS28 at the visit after the initiation of treatment was below 3.2 that indicates low disease activity. Regarding treatment adherence, only 8 patients (23%) were noncompliant, of which half for objective reasons, namely the unavailability of the drug in pharmacies at the time (MTX was unavailable for several months in Romanian pharmacies).

Further, our results showed that one in three patients experienced adverse reactions to therapy. The therapeutic agent that caused most adverse reactions was MTX (Figure 1).

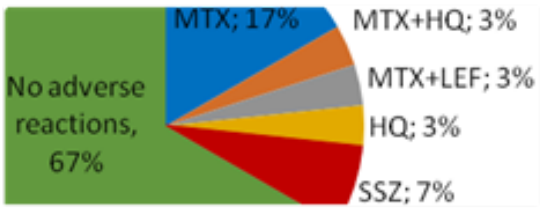

Figure 1.

The frequency of adverse reactions to conventional DMARDs prescribed to patients (MTX: methotrexate, HQ: hydroxychloroquine; LEF: leflunomide, SSZ: sulfasalazine)

In our group, adverse reactions reported by the patient or identified by the physician were not severe. The most common adverse reactions were muco-cutaneous in nature (mucositis, rash, pruritus) manifested in 20% of patients, followed by respiratory and digestive (dyspnoea, gastro-intestinal intolerance, increased transaminase level (≤ x2 times normal values) (Table II).

Table II

Distribution of adverse reactions to conventional DMARDs

DMARDs	The percentage of patients who experienced adverse reactions		
	Cutaneous	Respiratory	Digestive
MTX	11%	3%	3%
SSZ	3%		4%
HQ	3%		
MTX + HQ		3%	
MTX + LEF	3%		

In this retrospective study, we ascertained the treatment with conventional drugs in patients with newly diagnosed RA who were monitored in an outpatient clinic. In our cohort, the duration of the disease from diagnosis was about three years. This is considered important in therapy monitoring since, with increasing duration of time from diagnosis to initiation of therapy there is a decrease in treatment adherence [26].

According to the treatment guidelines developed by the EULAR and ACR [20], disease-modifying drugs are the basic treatment of RA. Even if DMARD therapy does not have a curative character), it is the most effective therapy in today's medical world, which reduces the inflammatory process and slows down the progression of destructive osteo-articular lesions to their complete stop [21, 25].

Although the optimal therapeutic approach to RA is not clearly defined and must be adapted to each individual, the effectiveness of starting DMARD therapy immediately after the onset of symptoms is generally recognized as essential. In RA treatment approach, physicians can use several treatment strategies, namely: sequential monotherapy, step-up combination therapy and induction therapy [13].

Sequential monotherapy consists of replacing an inefficient conventional agent, which had been prescribed initially, with another DMARD [25].

Step-up combination therapy consists of the addition of another DMARD to the originally prescribed agent when treatment response was unsatisfactory. This strategy has the advantage of introducing as many modifying agents as necessary, no agents being used in excess. The drawback is the presence of a time interval required for the new DMARD to exert its effect, meanwhile impeding sufficient disease control [25].

Induction therapy proved to be the most effective when compared to the other two types of therapy mentioned above, as demonstrated in randomized clinical trials, such as BEST [12], Fin-RACO [23], and Premier [5] trials. It consists of the initial administration of a combination of modifying agents. Once disease activity is controlled, the step-down approach is applied, which can reduce the number of DMARDs to a single agent. This strategy allows rapid and effective disease control, but exposes the patient to a high risk of toxicity and also has high costs.

Therefore, both step-up combination therapy and induction therapy (in case of severe disease) are reasonable therapeutic options in the management of RA [8].

Most patients in our study (83%) were treated since the baseline visit with a combination of CS DMARDs, in a step-up approach. Monotherapy versus combination therapy is still a widely-debated issue in medical literature [15]. While some clinical trials confirm the superiority of combination therapy (Best, FIN-RACo), others (TEAR [17] or SWEFOT [27]) demonstrated a good response to initial monotherapy with MTX, which can be subsequently adjusted in certain groups of patients with inadequate response. According to a randomized clinical trial conducted in The Netherlands and published in 2014 [7], triple therapy (MTX + SSZ + HQ) was identified to have superior clinical efficacy than MTX monotherapy, but for both cases radiographic progression was recorded after one year of treatment. A similar result was obtained in a study conducted on 1,100 patients in Columbia, where only 17% of patients received monotherapy [18]. The 2015 ACR recommendation for RA treatment point out that DMARD monotherapy (MTX preferred) is preferable to double or triple therapy [20].

In our group of patients, the initial treatment was effective in 53% of cases based on the value of DAS28 at the next visit. This shows the high rate of individual variability in reaching early response to treatment and the difficulty of establishing an optimal regimen since the diagnosis.

Regarding treatment adherence, only 23% of patients were noncompliant, but in the majority of cases it was due to the unavailability of the drug in pharmacies at that time (MTX).

In this study, 30% of patients experienced adverse reactions to therapy. The types of adverse reactions recorded were mild. The most common adverse reactions were muco-cutaneous, manifested in 20% of patients, followed by respiratory and digestive adverse reactions. The therapeutic agent that caused the most adverse reactions was MTX. This can also be explained by the fact that MTX was the most common drug prescribed in our group of patients.

MTX mainly caused muco-cutaneous (mucositis 11%), respiratory (dyspnoea 3%) and digestive adverse reactions (gastro-intestinal intolerance, increased transaminases level in 3%). These are also the most frequently reported adverse reactions cited in medical literature [4, 14]. In an observational trial conducted on 500 patients, the frequency of gastrointestinal adverse reactions and hepatotoxicity was greater than that of muco-cutaneous adverse reactions [10, 11]. There are pre-clinical observations that MTX-loaded liposomes may determine less toxic effects than MTX solutions.

Thus, this study has identified the following possible reasons of changing the initial treatment plan: lack of effectiveness (documented in nearly half of the patients in our group by the values of DAS28 higher than 3.2), the presence of adverse reactions (one third of cases) and noncompliance. Our results are supported by the patients` increased addressability, by the early diagnosis, early treatment of the disease and close monitoring of the patients in our study.

It is important to mention the limitations of this study. First, the number of cases might be insufficient to extrapolate the results to the entire RA population, given that the prevalence of RA is 1% in the general population), which accounts for about 3,000 cases in Cluj-Napoca. Second, the only adverse reactions that were identified by the attending physician were muco-cutaneous, and increased transaminases level, the others being reported by the patient. In some cases, we only had access to information upon patient presentation to the Department of Rheumatology of the Clinical Hospital for Infectious Diseases in Cluj-Napoca, which did not coincide with the onset of symptoms of the disease in all cases.

Conclusions

The most prescribed CS DMARDs in our cohort was MTX and the most used therapeutic strategy was step-up combination therapy. The initial treatment plan ensured the effective control of the disease in about half of RA patients and most of the patients were compliant with their treatment. The adverse reactions of CS DMARDs agents were not of vital importance, but determined the change of treatment.

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