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Evaluating the Effectiveness of Treatment of Methotrexate and Biological Agents in Hand Function and Deformities of Patients with Rheumatoid Arthritis

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Abstract

Objective: The study aims to estimate the types of hand deformities in patients with rheumatoid arthritis (RA) according to the mode of treatment. This includes conventional drugs DMARD or DMARD and biologic agents.

Methods: Sixty female patients who have been admitted to the Department of Rheumatology Central Clinical Hospital in Warsaw between February 2016 and July 2016 were included in this study. Patients were divided into two groups: 30 patients treated only with methotrexate (MTX), and 30 treated with MTX and biological agents. The control group included 30 healthy volunteers.

Results: Hand deformities recorded in 40% of cases in the group treated with MTX and biological agents and in 30% of cases treated with MTX monotherapy. The frequency of deformities were as follows: swan neck deformity (6.7%) in both groups, boutonniere deformity (20% and 23.3%), Z deformity (13.3 and 3.3%), ulnar deviation of the metacarpophalangeal joints (MCPJ) (10 and 13.3%), radial deviation of the wrist (6.7 and 13.3%), and sub-luxation of the MCPJ (20 and 10%).

It was observed that the maximum and average power grip strength, hand endurance, ability to rotate in the proximal and distal radio-ulnar joint were statistically significantly worse ($p < 0.0001$) in both RA groups compared to the control group. Between both RA groups, the group treated with MTX and biological agents showed statistically significantly better results in the average power grip strength ($p < 0.05$) and endurance ($p < 0.05$) in the dominant hand as well as in the non-dominant hand.

Conclusion: Biological treatment with MTX is more effective on the hands function than MTX monotherapy.

Keywords: Rheumatoid arthritis; Hand deformity; MTX; Biological agents; The Quality of grip; Handgrip strength

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects symmetrically small and medium sized joints. The typical joint involvement is the proximal interphalangeal (PIP) joints, the metacarpoophalangeal (MCP) joints, the wrists, the knees and the metatarsophalangeal (MTP) joints. Affected joints are swollen, painful and tender; the patient perceives stiffness with movement and limited motion. Distention of the joint capsule, ligament laxity, muscle imbalance, less motion in the joints and subluxations can lead to hand deformities in combination with external forces on the joints [1]. Deformation of hands is the cause of severe disability, resulting in the inability to grip. The patients cannot eat alone and need help in everyday life. The rheumatoid process destroys not only the joints but also the tendons, making it difficult to grip something. Chronic inflammation of the tendon sheaths and the degenerative changes in tendons and joint deformities may lead to spontaneous ruptures of tendons, which exacerbates dysfunctions of the hand.

The wrist

Typical deformities include shortening of the wrists, scapho-lunate dislocation, and carpal supination, translocation of the carpus in a lunar and volar direction, radial deviation of the carpus and dorsal subluxation of the ulnar. The extensor carpi-ulnaris tendon often subluxes volarly. The

characteristic Z deformity include: radial deviation at the wrist with ulnar deviation of the digits often with palmar subluxation of the proximal phalanges.

Radioscaphoid joint, which is the most important articulation of the carpal complex, is easily subjected to dislocation. Being the most mobile carpus, the scaphoid, with its elliptical facet, is easily misaligned within the distal radial facet as a result of abnormal joint motion. The increased ability for the wrist to undergo extension further exacerbates the problem. This results in the ulnar rotation of the scaphoid while displacing it palmarly [2].

Arthritis of the distal radio ulnar joint results in instability and dorsal subluxation of the ulnar head with a "piano key" movement upon downward pressure. A dorsally subluxated ulnar head with erosive abnormalities will often lead to rupture of neighbouring tendons [2].

The radial-wrist joint

The radial-wrist joint is one of the key elements determining the efficiency of the hand. The inflammatory process in the wrist causes the extensor tendon to deviate in the direction of the radial and dorsal band of the wrist and metacarpal. Radial deviation deformity consists of radial deviation in the radial-wrist joint and ulnar deviation of MCPJ in phalanges II-V. Destabilization of the joints plays an important role in this deformity. The scaphoid bone is set in palmar flexion, losing its role of stabilization. This results in translocation of the bone towards the radial styloid. Changes in the muscles in the hand result in their decreased role in stabilization. Radioulnar synovitis sometimes causes further changes in the ulnar collateral ligaments of the wrist associated with tendon ulnaris [3].

MCP joints

The MCP joints strengthen the longitudinal and transverse arch systems of the hand. The most frequent deformity of the hand affects the MCP joint and it is characterized by a volar subluxation of the proximal phalanges and ulnar drift of the finger [4]. This ulnar deviation of the MCP joint is usually caused by chronic synovitis, which disrupts the ligamentous support of the joint [4]. Consequently, the radial stress on the fingers with pinch drives the fingers in an ulnar direction. Patients with this deformity often report inability to extend the fingers. The ulnar deviation of the fingers is a consequence of imbalance of muscle strength between extensors and flexors of the radial and ulnar side of the wrist and fingers. The rheumatoid process progresses to further deform the hands, from interosseous and lumbrical muscle atrophy, to hypertrophic changes in the proximal interphalangeal and distal interphalangeal joint contractures. Ulnar deviation of the fingers is caused by insufficiency of the first interosseous muscles, the tendon flexors and extensors, which pull the fingers towards the ulnar, stretching the MCP joint capsule and ligaments to the radial side, shortening the interosseous muscles on the ulnar side, shortening the abductor finger V and dislocating the extensor tendons between the head of the metacarpal bones [4].

The thumb

Thumb deformity is determined by a complex interaction of the primary joints, tendon function and integrity. Joints adjacent to the primary affected joint usually assume an opposite angle. If they do not, tendon ruptures should be suspected [5].

The boutonniere deformity is the most common rheumatoid thumb deformity. This consists of MCP joint flexion and IP joint hyperextension with a consequent loss of thumb mobility and pinch. The pathology of this deformity usually starts with MCP joint synovitis stretching the dorsal capsule. The overlying extensor hood and extensor pollicis brevis tendon insertion become loosened, resulting in loss of MCP joint extension and volar subluxation of the base of the proximal phalanx. The extensor pollicis longus tendon displaces ulnarly and volar onto the axis of rotation. Each time the patient pinches the thumb, a cycle of MP joint flexion and IP joint hyperextension is initiated. In time, the IP joint deformity approximates the MP joint deformity, and the result is often a 90°/90° deformity [5].

Swan neck deformity starts at the carpometacarpal (CMC) joint with subluxation of the first metacarpal, which then assumes an adducted and flexed position. After CMC joint subluxation and metacarpal flexion and adduction is MCP joint hyperextension and distal joint flexion. This deformity is the opposite of the common boutonniere deformity. The dorsoradial subluxation and dislocation occurs as the thumb is pinched during daily activities. With the metacarpal base subluxed radially, the abduction forces are reduced and a progressive adduction and flexion contracture of the metacarpal develops.

The extensor pollicis longus (EPL) is the most likely flexor tendon to rupture in rheumatoid patients. Rupture of the EPL occurs from infiltrative tenosynovitis. The functional loss varies and the tendon rupture may go undetected for some time.

Inflammatory changes of the thumb joints lead to loss of resistance, and consequently to loss of function of the hand grip (monkey grip). Deformity of thumb plays an important role, because the efficiency of the whole hand is 40-50% dependent on the actions of the thumb [6].

The fingers

Besides the ulnar deviation of fingers, the swan neck finger (SN) and the Boutonniere (BN) finger are the most common deformities detected in RA patients [7].

Flexion and extension contracture in the proximal and distal interphalangeal joint of the fingers lead to characteristic swan-neck deformity (flexion contracture at the DIP and hyperextension at the PIP) or boutonniere deformity (flexion contracture at the PIP and hyperextension at the DIP). The pathology of swan-neck deformity is initiated at the level MCP, while the pathology of the boutonniere deformity begins with synovitis of the PIP joint, followed by elongation of the central slip, subluxation of the lateral bands, and contracture of the retinacular ligament.

The SN deformity (SND): is characterized by a flexion of both MCP and DIP joints associated with the hyperextension of the PIP joint [8]. The SND represents the result of pathology involving MCP, PIP, and DIP joints and the wrist [9]. Synovitis of the MCP joint causes alteration of the volar plate, determining MCP joint subluxation and it produces a shortening of the intrinsic muscles leading to PIP hyperextension. Moreover, synovitis of the MCP joint produces an alteration of the insertion of the long extensors on the dorsal base of the proximal phalanx, producing hyperextension of the PIP joint. The deformity of the PIP joint is the result of the transfer of the extensor force to the base of the middle phalanx. Synovitis of the PIP joint can extend to FDS tendons and joint collateral ligaments. This synovitis produces degeneration of the FDS insertion and of

the volar plate and collateral ligaments. It ultimately determines abnormal hyperextension of the PIP joint because of the action of the extensor forces [8]. Synovitis of the DIP joint produces the rupture of the terminal extensor tendon insertion. The volar supporting structures of the PIP joint are damaged because the extensor forces are modified, leading to PIP joint hyperextension. The swan neck finger is the most severe deformation in RA.

Deformation of SND significantly limits the ability to grip. Hand movement ability is reduced by half. In this deformity the proximal phalanx and middle phalanx do not participate in the grip. This is often accompanied by ulnar deviation of fingers. This results in fixed hyperextension of the PIP joints, changing their anatomy and leading to a reduction in the gripping force. Thus, both the quality of the grip and grip strength are limited.

Boutonniere deformity (BND): is characterized by extension of both MCP and DIP joint associated with a flexion deformity of the PIP joint [10]. The BND is caused by intra-articular proliferation of the synovium of the PIP joint, which distends the capsuloligamentous apparatus, leading to extension of both MCP and DIP joints associated with a flexion deformity of the PIP joint [8]. Small degree of BND does not affect the activity of a finger, but contracture greater than 90 percent prevents full opening of the hand and grasping larger objects. BND occurs in the phalanges II-V.

Handgrip is a useful parameter of evaluation in RA patients, since muscle weakness is a common symptom. One of the most important problems of rheumatoid hands is the reduced possibility of gripping. Impairment of grip is due to the limitation of joint mobility in PIP, DIP and MCP joints. Decreasing movement of the interphalangeal joint reduces the grip less than the changes in the MCP joint. There are three main reasons for the limitation of grip: joints, ligaments and muscles.

1. The joint mechanism consists of a joint surface deformation or joint capsule contracture.

2. The ligament mechanism depends on contracture of collateral ligaments in the MCP joint.

In the normal state, ligaments are relaxed in extension, while contract as the proximal phalanx bends, increasing the pressure of the articular surface and thereby improving grip strength. During contractures, tension of ligaments rapidly increases during bend tests, so that the function of the hand grip is limited. Limitation of grip may be the result of contracture of two muscle groups, both internal and external.

Hand gripping plays a role in performing everyday activities. The hand grip is a tool that enables objects to be grasped and manipulated. The proper functioning of the hand consists of 3 elements:

1. Grip quality

2. Grip value

3. Ability to handle the arm.

Grip quality means the ability to adapt to the shape of a hand-held object. Types of grip can be compared to the shale of various tools such as a hook, ring, pincers and pliers. The value of the hand grip means the ability to carry an external load. This depends on not only muscle strength, but also the efficiency of the ligaments, and even friction between the hand and the held object. The direction of external force acting on the hand plays an important role.

Most of the activities of daily living are activities that require the participation of both hands. Usually one of them (called dominant), performs basic tasks, while the second (auxiliary), is used only to aid for example to hold down (stabilize) an object. Sometimes the role of both hands is identical-e.g. bimanual, handling large objects.

An efficient grip occurs only if the correct anatomy is present in the hand, the mobility of its components is not impaired and the nervous system is not damaged. Hand grip consists of strength, mobility and touch.

Grip strength is different grip types (power grip, key pinch, precision pinch and tripod pinch).

The aim of the study was to assess the types of hand deformities and the effectiveness of the hands in patients with rheumatoid arthritis (RA) treated with MTX monotherapy or with MTX in combinations with biologic agents.

Methods

Patients

Sixty RA seropositive female patients were enrolled in the study, 30 patients were treated with methotrexate alone and 30 with methotrexate and biological agents. The patients were admitted to the Department of Rheumatology and Internal Diseases of Central Clinical Hospital in Warsaw from February 2016 to July 2016**.**

A detailed history was taken and full clinical examination was done. The hands were examined to detect a dominant and non-dominant hand, the presence of swan-neck deformity, boutonniere deformity, Z deformity of the thumb, radial deviation of the wrist joint, ulnar deviation of the MCP joints, subluxation of the wrist and subluxation of the MCP joints, and handgrip strength.

The control group consisted of 30 female volunteer workers from the hospital.

The present study was approved by the local research ethics committee (protocol number 42/2015), and all the subjects signed a free informed consent from before participating in the study.

Assessment

All patients fulfilled the 2010 ACR classification criteria for RA [11]. A protocol was designed to record age, duration of the disease, rheumatoid factor, antibodies against citrullinated peptide (anti-CCP)**,** stage of RA according to Larsen and Dale [12], SNJ, PNJ, DAS28 [13], VAS (pain), VAS (disease activity), HAQ [14] and types of deformities.

Radiographic damage was evaluated according to Larsen and Dale [12].

All of the women answered the Health Assessment Questionnaire (HAQ) [14] and were submitted to evaluate handgrip strengths.

To measure the handgrip, we used the standard adjustable-handle Jamar hydraulic dynamometer (model 18937009) at (Kg) scale. For standardization, it was set at the second handle position for all subjects as suggested by the American Society of Hand Therapists [15]. The handgrip strengths of dominant and non-dominant hands were measured with the subjects seated on a chair, hips and knees flexed at 90°, feet kept on the floor, upper limbs in adduction position, elbow at 90° and wrists in neutral position. Each woman performed three sustained contractions for 6-s, with a 30-s rest interval between each contraction for both handgrip. A mean value was obtained from

Table 1: Baseline demographic and clinical characteristics of study population.

Parameters	MTX+biological agent group	MTX group	Control group	P
Age	51.2±13.0	55.9±10.6	50.5±11.1	0.1554
Female	30 (100%)	30 (100%)	30 (100%)	
BMI	26.6±5,5	27.0±6.5	27.3±5.6	0.9028
Intellectual work	18 (60%)	15 (50%)	13 (43.3%)	0.4300
Right hand dominance	30 (100%)	30 (100%)	30 (100%)	1.0000
RA duration	12.10±6,6	10.5±8,4	-	0.4044
Stage III	27 (90%)	27(90%)	-	1.0000
Stage IV	3 (10%)	3 (10%)	-	
DAS 28	3.25±1,29	4.43±1,20	-	**0.0006**
Tender joint	2.0 [0.0–6.0]	6.5 [3.0–10.0]	-	**0.0035**
Swollen joint	1.5 [0.0-2.0]	1.5 [0.0-2.0]	-	**1.0000**
VAS (pain)	19.5±18.7	40.8±21.9	-	**0.0024**
VAS (disease activity)	27.3±20.6	44.8±19.5	-	**0.0013**
HAQ	0.65±0.58	1.09±0.61	-	**0.0063**

Table 2: Values of laboratory data in RA patients.

Parameters	MTX+biological agent group	MTX group	P
RF	21.4 [9.75 – 168.5]	64.3 [11.4 – 183.0]	0.3601
ESR (mm/h)	21.5±16.2	36.3±27.6	**0.0146**
CRP (mg/l)	4.7 [2.1-11.8]	9.1 [4.3-29.5]	**0.0422**
Leukocytem (G/l)	7.49±2.04	7.76±2.28	0.6287
Erythrocytes (T/l)	4.44±0.27	4.19±0.45	**0.0127**
Hemoglobin (g/l)	13.29±1.04	12.1±1.6	**0.0009**
Thrombocytes (G/l)	305.6±70.0	297.9±82.4	0.6980
AspAT (U/l)	21.6±8.0	20.5±11.9	0.6758
AlAT (U/l)	26.0±16.7	20.2±12.3	0.1304
Bilirubin (mg/dl)	0.40±0.18	0.43±0.17	0.4505
Creatinine (mg/dl)	0.70±0.16	0.72±0.12	0.6244
eGFR (ml/min)	88.7±20.0	91.9±20.5	0.5468

Table 3: Distribution of the different combinations of hand deformities.

Hand deformity	MTX+biological agents group	MTX group	P
Swan neck fingers II–V	2 (6.7%)	2 (6.7%)	1.000
Z deformity of thumb	4 (13.3%)	1 (3.3%)	0.3533
Buttonniere fingers II–V	6 (20.0%)	7 (23.3%)	0.7540
Buttonniere thumb	2 (6.7%)	4 (13.3%)	0.6707
Ulnar deviation of the wrist joint	3 (10.0%)	1 (3.3%)	0.6120
Radial deviation of the wrist joint	2 (6.7%)	4 (13.3%)	0.6707
Ulnar deviation of II-V MCP joints	3 (10.0%)	4 (13.3%)	1.000
Subluxation of wrist joint	2 (6.7%)	2 (6.7%)	1.000
Subluxation of MCP joint of II-V fingers	6 (20.0%)	3 (10.0%)	0.4716
All deformities	30	28	NS

Swan neck - hyperextension of the proximal interphalangeal joint with flexion of distal interphalangeal joint.
Boutonniere finger – flexion of the proximal interphalangeal joint with hyperextension of distal interphalangeal joint.
Z-deformity of thumb – flexion of the metacarpophalangeal joint and hyperextension of the interphalangeal joint.
Ulnar deviation – ulnar deviation of metacarpophalangeal joints.

the three measurements. All evaluations were made by only one examiner.

The subjects sat with their shoulders adducted and neutrally rotated, elbows flexed at 90° and forearms and wrists in neutral position. They were then to grip with maximal effort for 3s. Verbal encouragement was given consistently throughout all measurements. For scores of three consecutive trials were recorded for each strength test for each hand. An average of these three trials and the highest

grip strength for each hand was used for analysis. The trials for each measurement were separated by a rest of at least one minute to minimize fatigue.

Hand endurance was measured using a dynanometer. The examination depended on recording the amount of time (in seconds) the patient was able to grip the dynanometer using maximum effort. The normal standard was set as 6-s before the examination. Next, the manipulate ability of the hands was assessed. This was done by recording the maximum number of rotations done by patient in the proximal and distal radioulnar joint, over the time span of 10-s. This was done 3 times and the number of rotations was recorded.

Effectiveness was defined as the achievement of the hands grip strength of greater than 10 kg.

HAQ was applied because of its validity [14] and usefulness for the assessment of the functional capacity of RA patients. This questionnaire was individually applied to every woman in a single day. In case of doubt, the interviewer repeated the question only once and slowly.

Body weight and height were measured during the exam and values were expressed as kilograms and centimeters, respectively. To calculate BMI, height was converted into meters (BMI= weight/height^2).

Laboratory test

Blood was collected after 4h fasting for analysis of the erythrocyte sedimentation rate (ESR) (Westergren, mm/l), the morphology composition of peripheral blood, C-reactive protein (CRP) (mg/l), bilirubin (mg/dl), AspAT (U/l), AlAT (U/l), creatinine (mg/dl), eGFR (ml/min), rheumatoid factor (RF) (IU/ml) and anti-CCP (IU/ml) within the Central Diagnostic Laboratory of the Central Clinical Hospital. The glomerular filtration rate (GFR) was calculated from the Cockroft-Goult's formula.

Pharmacological treatment

In the first group, patients were treated with MTX as DMARD in doses of 25 mg per week orally.

In the second group, besides MTX (as DMARD) patients were given the following biological agents:

TNF inhibitors 24 (infliximab – 4, adalimumab 10, golimumab 6, certolizumab 2, etanercept 2), tocilizumab – 4, rituximab 2.

Statistical analysis

Statistical analysis was done with the statistical packet SPSS/PC+. The following tests were applied:

1. A value for an average continuous variable was assessed on the basis of the ANOVA test. Post-hock analysis were performed with

Table 4: Number and % of patients without deformity, with a single deformity and with more than one deformity.

Parameters	MTX+biological agents group	MTX group	P
Without deformity	18 (60.0%)	21 (70.0%)	0.7480
Single deformity	5 (16.7%)	3 (10.0%)	
More than one deformity	7 (23.3%)	6 (20.0%)	

Table 5: The comparison of grip strength, hand endurance measurement in seconds, and manipulation ability of hands.

	MTXbiologic agent (1)	MTX (2)	Control (3)	ANOVA 1 *vs.* 2 *vs.* 3	1 vs 2	1 vs 3	2 vs 3
Power grip strength was measured with a dynamometer							
Right hand	kg	kg	kg	P	p	p	P
Maximum	19.7±10.8	13.2±7.4	40.5±13.0	**<0.0001**	0.0546	**<0.0001**	**<0.0001**
Average	18.2±10.8	11.5±6.7	38.8±12.2	**<0.0001**	**0.0344**	**<0.0001**	**<0.0001**
Left hand							
Maximum	18.8±11.0	14.5±7.4	36.2±10.9	**<0.0001**	0.2133	**<0.0001**	**<0.0001**
Average	17.9±10.3	11.9±6.3	37.2±11.2	**<0.0001**	**0.0410**	**<0.0001**	**<0.0001**
Hand endurance measured with a dynamometer							
Right hand	s	s	S	p	p	p	p
Maximum	47.1±20.8	36.8±23.5	60.0±0	**<0.0001**	0.0770	**0.0195**	**<0.0001**
Average	45.3±21.8	32.4±23.4	60.0±0	**<0.0001**	**0.0231**	**0.0076**	**<0.0001**
Left hand							
Maximum	45.9±20.6	36.2±22.7	60.0±0	**<0.0001**	0.0907	**0.0077**	**<0.0001**
Average	44.7±21.3	32.1±23.1	60.0±0	**<0.0001**	**0.0230**	**0.0045**	**<0.0001**
Number of rotation in radio-ulnar proximal and distal joints (hand manipulation ability)							
Right hand	Number of rotation in 10 s	N of rotation in 10 s	N of rotation In 10 s	p	p	p	P
Maximum	7.8±3.6	4.8±2.3	12.3±2.9	**<0.0001**	**0.0006**	**<0.0001**	**<0.0001**
Average	7.2±3.5	4.4±2.3	11.4±2.6	**<0.0001**	**0.0008**	**<0.0001**	**<0./0001**
Left hand							
Maximum	7.0±3.3	4.9±2.2	11.0±2.9	**<0.0001**	**0.0173**	**<0.0001**	**<0.0001**
Average	6.9±3.3	4.5±2.2	10.9±2.5	**<0.0001**	**0.0021**	**<0.0001**	**<0.0001**

Tukey's test.

2. The Chi square test or the Fisher's exact test was used to check the discreet variables, presented in number and proportion. The threshold of significance used was 5%.

3. Multiple logistic regression analyses were performed to evaluate the efficacy of biologics agents *vs.* MTX alone on hand grip strength, after adjusting for confounders: age, BMI and RA duration.

4. Pearson's or Spearman's correlation coefficients were calculated.

Results

Demographic and clinical characteristics of the study groups are shown in (Table 1). All RA female patients had RF and anti-CCP positive values.

No statistically significant differences were found between the examined RA groups apart from the DAS 28 value and HAQ, which were statistically significant lower in the "MTX and biological agent" group. All female patients had the right hand as dominant.

Values of laboratory data are shown in (Table 2). There was a statistically significant difference between the average values ESR, CRP, erythrocytes and hemoglobin in both RA groups. In the "MTX and biological agent" group there were a statistically significant lower value of ESR, CRP and a statistically significant higher value of erythrocytes and hemoglobin.

Hand deformities recorded in 40% of cases in the group treated with MTX and biological agents and in 30% of cases treated with MTX only. The frequency of deformities was as follow: swan neck deformity (6.7%) in both group, boutonniere deformity (20% and 23.3%), Z deformity (13.3 and 3.3%), ulnar deviation of the MCPJ (10 and 13.3%), radial deviation of the wrist (6.7 and 13.3%), and subluxation of the MCPJ (20 and 10%).

Distribution of the different combination of hand deformities are shown in (Table 3 and 4). No statistically significant differences were found between examined RA groups and with the different combination of hand deformities.

The power grip strength, hand endurance and hand manipulation ability was compared between the RA groups and the control group and the results are show in (Table 5). It was observed that the maximum and average power grip strength, hand endurance, ability to rotate in the proximal and distal radio-ulnar joint were statistically significantly worse in both RA groups compared to the control group ($p< 0.0001$). Between both RA groups, the group treated with MTX and biological agents showed statistically significantly better results in the average power grip strength and endurance in the dominant hand as well as in the non-dominant hand ($p< 0.05$).

Efficiency obtained in patients treated with MTX and biologics agents was statistically significant higher than in the group of patients receiving MTX monotherapy (73.3% *vs.* 40%, p=0.0092).

In multivariable analysis model (adjusted for age, BMI and RA duration) taking MTX and biological agents was an independent predictor of effectiveness. Analysis yield that the efficacy of the MTX and biologics agents was more than 4 times better than MTX monotherapy (adjusted OR: 4.64, 95% CI: 1.42 – 15.19). Results are shown in (Table 6).

Table 6: Multiple logistic regression for evaluate the effectiveness of biologics agents on hands grip strength.

Parameters	OR [95% CI]	P
Biological agents *vs.* MTX alone	4.64 [1.42–15.19]	0.0110
Age (per 10-year increase)	0.95 [0.56–1.62]	0.851
BMI (per 1 increase)	0.96 [0.87–1.06]	0.434
RA duration (per 1 year)	0.94 [0.86–1.03]	0.196

In the MTX and biological agents group there was strong negative correlation between the power grip strength, hand endurance, hand manipulation ability and the index of disease activity DAS 28 (Pearson's correlation coefficient between r = -0.38 and r = -0.75, $p< 0.05$), (Table 7).

Discussion

Rheumatoid arthritis (RA) is a chronic inflammatory disease, which affects 1% of the US population, and approximately 70% of RA patients develop pathologies of the hand, especially of the MCP joints, the extensor and flexor tendons of the fingers are also frequently involved [16]. Wrist involvement is seen in up to 50% of patients within 2 years of diagnosis and in up to 90% of patients following diagnosis [17].

Hand deformities in rheumatoid arthritis have negative impact on the quality of life of RA patients [18]. Unfortunately, RA usually leads to progressive deterioration of hand function [19, 20]. Until recently, the rate of permanent work disability has been high despite development of anti rheumatic therapy. Joint damage progresses constantly over the first 20 year of RA. It accounts for about 25% of disability in established RA [18].

In our study we examined RA patients, who underwent biological DMARDs. We assessed deformities of hands and compared this group patients with RA patients treated with MTX only. We observed statistically significant lower the DAS 28 values, and a lower number of swollen and tender joints in the "MTX with biological agent" group therefore it is no surprising, as we know their strong anti-inflammatory action. There was also a statistically significant difference between the average values of ESR, CRP, erythrocytes and hemoglobin. In the "MTX with biological agent" group there were statistically significant lower values of ESR, CRP and a statistically significant higher values of erythrocytes and hemoglobin therefore this additionally confirms their strong anti-inflammatory action.

Twelve (40%) patients with MTX and biological agents group developed at least one hand deformity and 28 deformities were observed in the MTX monotherapy group. The disease duration in our patients was similar so the differences are the results of modes of treatment. Logistic regression analysis shown that the efficacy of the biologics agents was more than 4 times better than MTX monotherapy.

Horsten et al. [21] in their study determined the prevalence of hand and wrist symptoms and impairments, and the resulting activity limitations in relation to disease duration in patients with rheumatoid arthritis. A cross-sectional study included 200 consecutive RA patients in 4 categories of disease duration: 2-4, 4-6, 6-8 and ≥8 years. Patients were asked about the presence of various hand and wrist symptoms, and underwent a standardized physical examination. To evaluate limitations, patients completed the Disabilities of the Arm Shoulder and Hand questionnaire and scored their limitations on a

Table 7: The correlation between hands function (grip strength, hand endurance measurement in seconds) and age, RA duration and DAS 28.

	MTX+BIO group N=30			MTX group, n=30		
Parameters	Age	RA duration	DAS28	Age	RA duration	DAS28
Maximum, right hand	r= -0.24 p=0.19	r= -0.27 p=0.14	**r= -0.47 p=0.0075**	r=0.05 p=0.78	r= -0.32 p=0.08	r= -0.35 p=0.06
Average, right hand	r= -0.26 P=0.16	r= -0.30 p=0.11	**r= -0.50 P=0.0051**	r=0.07 P=0.70	R= -0.26 p=0.16	**r= -0.38 P=0.0430**
Maximum, left hand	r= -0.12 p=0.54	r= -0.18 p=0.35	**r= -0.39 p=0.0321**	r=0.17 p=0.37	r= -0.11 p=0.57	r= -0.26 p=0.17
Average, left hand	r= -0.23 P=0.22	r= -0.26 p=0.16	**r= -0.48 P=0.0071**	r=0.13 P=0.50	r= -0.20 p=0.28	r= -0.36 p=0.0562
Maximum, right hand	**r= -0.47 p=0.0087**	r= -0.12 p=0.55	**r=-0.69 p<0.0001**	r= -0.34 p=0.06	r= -0.24 p=0.19	r= -0.29 p=0.13
Average, right hand	**r= -0.50 P=0.0047**	r= -0.13 p=0.49	**r= -0.68 P<0.0001**	r= -0.28 P=0.14	r= -0.26 p=0.16	r= -0.26 P=0.17
Maximum, left hand	**r= -0.54 p=0.0020**	r= -0.07 p=0.72	**r= -0.75 p<0.0001**	r= -0.27 p=0.140	r= -0.19 p=0.31	r= -0.30 p=0.11
Average, left hand	**r= -0.50 P=0.0046**	r= -0.11 p=0.58	**r= -0.71 P<0.0001**	r=-0.26 P=0.17	r= -0.22 p=0.25	r= -0.27 P=0.16

Numerical Rating Scale from 0 to 10. Of all patients, 94% suffered from at least one symptom, and 67% had at least one impairment, mostly from the earliest stages onwards. A high prevalence of hand and wrist symptoms and impairments is often already present after 2 years of disease duration, but the mode of treatment was not analyzed in this study.

In our study we compared the grip strength, hand endurance measured with a dynamometer and number of rotation in radio-ulnar proximal and distal joints in RA groups and in the control group. Better results were observed in patients treated more aggressively, with MTX as well as biological agents.

Bodur et al. [22] in their study assessed grip strength, lateral, tip and three-fingered pinch in 105 RA patients, comprising 84 females and 21 males with a mean age of 49.4 years and disease duration of 7.6±6.1 years. Of the patients, 74.3% were seropositive and 25.7% were seronegative. Disease duration, grip strength, pinch measurement, clinical and laboratory activity parameters were strongly correlated with hand disability. Hand disability was more related to disease activity parameters than articular damage. Grip strength and pinch measurements were the most related parameters with hand disability. The authors also did not analyze the mode of treatment in their groups of patients.

Slowing down the disease progression is one of the most important aspects of managing RA and could increase patient's quality of life. Since wrist, hands and finger joints are generally affected in this condition, the mode of treatment have an important role, but it was not analyzed in the following papers [23-26].

A very interesting paper written by Johnsson and Eberhards [23] stated that more than half of the patients in early RA had developed hand deformities after 10 years. The most prevalent deformities are ulnar deviation of the MCP joints, button hole deformity and swan neck deformity. The majority of deformities occurred during the first years of disease. Presence of hand deformities had an impact on daily life function and added useful prognostic information, being an early sign of a more severe disease.

Cima et al. [24] cited that functional performance in RA hands is correlated with the grip strength. In their group of RA female patients with the mean age 53 the mean handgrip strength of a dominant hand was 12 kg.

In our female RA patients treated with MTX and with biological agents the mean value of handgrip strength of a dominant hand was 18.2 kg, in the second group treated only with MTX the mean handgrip strength was 11.5 kg was 11.5 kg.

In our female RA patients group treated with MTX and with biological agents the maximum value of handgrip strength of a dominant hand was 19.7 kg, in the second group treated only with MTX it was 13.2 kg, but in control group 40.5 kg was recorded.

Bergstra et al. [25] cited that in the literature the maximum strength for a healthy woman aged 50–54 years was reported to be 33.7 kg for power grip. According to Gunther et al. [26], which examined grip strength in healthy Caucasian adults, they stated that grip strength is significantly less in women than in men. Observed values in women ranged between 9 kg and 51 kg (right hand) and 7 kg and 45 kg (left hand). In both women and men, they observed an increase of grip strength until a maximum around the age of 35 years. Further on, increasing age was inversely related with grip strength. Grip strength is significantly higher in the right hand in both sexes. Mean values in women are 29±7 kg for the right hand and 27±7 kg for the left hand, thus strength of the left hand averages 95% of the right hand. Patients with RA are known to have lower grip strength compared to age and sex matched control [21].

Dedeoglu et al. [27] found in their study that hand grip and pinch strengths were negatively correlated with the disease activity, articular damage, pain, disease duration, functional impairment and disability in RA patients. The strength of the study is that they examined pinch strength, but the limitation was not analyzed the treatment of patients.

Another very interesting paper estimates changes in early rheumatoid hands. Sheehy et al. [28] concluded, that hand grip testing and subsequent conversion to z scores corrected for age and gender correlate with disease activity in early RA. They have shown that the grip strength z scores can discriminate between various disease states and the strength seems to return to near normative data when the disease is in remission. Bjork et al. [29] assessed hand function in women and men with early rheumatoid arthritis. In their prospective study over three years (the Swedish TIRA project) they stated that hand function was profoundly affected at diagnosis of RA, but improved significantly within 3 months and remained stable (but still affected) over 3 years. As expected, women on average had significantly lower grip force than men.

Adams and Burridge [30] in their study concluded that in the early RA population handgrip strength as an accurate indicator of upper limb ability. Ulnar deviation at the MCP joints shows only a weak to moderate association with upper limb functional activity

and ability. Although the Disability of the Arm, Shoulder and Hand (DASH) questionnaire and the Grip Ability Test (GAT) were strongly correlated, the DASH was a more discriminating measure than the GAT in assessing upper limb ability in this sample population.

The aim of study of Eberhardt et al. [31] was to assess the usefulness of hand function measurements and the treatment effects of tumour necrosis factor (TNF) blockers. Moreover they analyzed the relationship between different hand function tests and also relate hand function to general disability and disease activity. The study group consisted of 49 patients with established RA who were followed for 1 year while on TNF inhibitors. HAQ, DAS28, grip and pinch force, and GAT showed a highly significant improvement over time. The authors concluded that patients with advanced RA attained considerable improvement in hand function that was only partly reflected by measures of general disability and disease activity. Our conclusion is similar to conclusion of Eberhardt. We conclude that biological treatment with MTX is more effective on the hands function than MTX monotherapy.

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