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Original Scientific Paper

USE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN PATIENTS WITH ADVANCED ACTIVE RHEUMATOID ARTHRITIS

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SUMMARY – This study aimed to determine whether patients with active rheumatoid arthritis (RA) regularly take non-steroidal anti-inflammatory drugs (NSAIDs) and to clarify whether their decision to take NSAIDs depends on disease activity, intensity of pain, or functional status. The study also aimed to identify the risk factors for gastrointestinal side effects. Over 6 months, we conducted a cross-sectional single-center study of consecutively hospitalized patients with confirmed RA. Activities of daily living, pain intensity, and disease activity were evaluated by the Health Assessment Questionnaire, visual analog scale, and disease activity score, respectively, in 28 joints. Of 73 patients diagnosed with RA, 48 (66%) regularly took NSAIDs. Compared to non-users, NSAID users used glucocorticoids less frequently. The decision to use NSAIDs was independent of disease activity, pain intensity, degree of functional impairment, or presence of gastrointestinal risk factors. However, a higher degree of functional impairment was associated with a longer duration of continuous NSAID and glucocorticoid use. NSAIDs are still relevant for RA treatment. The decision to use them is not necessarily affected by disease activity or pain intensity, but their prolonged use is required in patients with a higher degree of functional disability. NSAIDs enable exclusion of glucocorticoid use, sparing patients of glucocorticoid-related side effects.

Key words: *Rheumatoid arthritis; Non-steroidal anti-inflammatory drugs; Gastrointestinal side effects; Glucocorticoids; Disease activity*

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatic disease the key clinical manifestations of which include pain and functional impairment[1]. Several factors are associated with

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an increased risk of RA, including female gender and smoking[2].

The last decade has seen many advances in RA treatment, such as disease-modifying antirheumatic drugs (DMARDs), which may be synthetic (conventional, csDMARDs) or biologic (bDMARDs)[3].

Beyond csDMARDs and bDMARDs, non-steroidal anti-inflammatory drugs (NSAIDs) are available for RA treatment[4]. For the past 50 years, they have been at the forefront of symptomatic RA treatment because of their ability to produce an analgesic effect, even with lower doses, and an anti-inflammatory effect, with maximum daily doses. The effectiveness of all NSAIDs has been found to be the same in population studies, although with individually variable efficacy and tolerability[5-8]. The basic mechanism of action of NSAIDs is through inhibition of the cyclooxygenase (COX) enzyme, which catalyzes transformation of arachidonic acid into prostaglandins and thromboxane. All standard NSAIDs equally inhibit COX-2, on which their therapeutic effect is based, while the occurrence of gastrointestinal side effects depends on their degree of COX-1 inhibition[9-14]. NSAIDs cause both minor gastrointestinal side effects and serious gastrointestinal events such as ulcers and bleeding[15-20]. There is evidence that every year, 1.3% of RA patients on NSAID therapy develop serious gastrointestinal complications. Furthermore, there is significant evidence that 81% of patients with RA hospitalization due to a serious gastrointestinal complication related to NSAID use did not have dyspeptic symptoms[21,22].

Our study aimed to investigate the presence of NSAIDs in the treatment of RA patients with active disease and significant pain, in order to evaluate if NSAID use depends on pain intensity, disease activity, or degree of functional impairment. We also aimed to ascertain if NSAID use is associated with the presence of risk factors for gastrointestinal side effects.

Patients and Methods

This study was conducted at the Department of Rheumatic Diseases and Rehabilitation, University of Zagreb, School of Medicine. Seventy-three consecutive patients with RA that were hospitalized to re-evaluate their therapy and achieve better RA control were included in the study. The diagnosis of RA was established according to the Revised American College of Rheumatology classification criteria[23].

The study was conducted in accordance with the Principles of Good Clinical Practice and standards for the protection of human patients participating in biomedical research, and was approved by the institutional Review Board. Upon signing an informed consent form for inclusion into the study, patients were required to answer a series of questions regarding their current RA therapy, duration of therapy, dosage, presence of risk factors for gastrointestinal side effects, use of gastroprotective medications, and whether or not they were currently experiencing any gastrointestinal side effects.

In this study, the presence or absence of the following risk factors for NSAID-related gastrointestinal side effects was evaluated: age >65 years, positive medical history of ulcer, simultaneous use of NSAID and anticoagulants, simultaneous use of NSAID and glucocorticoids, simultaneous use of NSAID and acetylsalicylic acid (ASA) in cardioprotective dosage. Gastrointestinal risk factors were graded according to the association between each factor and side effects using a grading protocol designed by the Department of Rheumatology with the hospitalized patients/study population (Table 1).

Activities of daily living were assessed using the Health Assessment Questionnaire (HAQ)[24]. Pain intensity was measured using the numerical rating scale (NRS)[25]. Patients maintained a pain diary in which they rated their pain with the NRS every 2 hours. For every patient, an average value during hospital stay was calculated. Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28)[26]. An overall DAS28 index of >5.1 is considered highly active disease. Other data were obtained from patient files, charts, and personal pain journals.

Statistical analysis

The normality of distribution of numerical variables was tested using the Kolmogorov-Smirnov test. Normally distributed numerical variables were presented as mean ± standard deviation (SD) and non-normally distributed variables were presented as median and interquartile range (IQR). Categorical variables were presented as proportions. The t-test, Mann-Whitney U-test, Fisher test, χ^2-test, Pearson's

Table 1. Risk factors in study patients graded according to association of each factor and side effects as implemented at Department of Rheumatology

Factors increasing GI risk of NSAID side effects	Points
History of ulcer	
History of ulcer (complications or no complications)	4
Dyspeptic symptoms (GERD, gastritis)	3
No history of ulcer	0
Age (years)	
<45	0
45-60	1
60-70	2
>70	3
Simultaneous usage of NSAID and anticoagulants	
Yes	3
No	0
Simultaneous usage of NSAID and GC	
Yes	2
No	0
Simultaneous usage of NSAID and ASA in cardioprotective dosage	
Yes	2
No	0

GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drugs; GERD = gastroesophageal reflux disease; GC = glucocorticoid; ASA = acetylsalicylic acid; 0 = lower risk factor score; 14 = highest risk factor score

correlation, and Spearman's rank correlation were appropriate, but the results obtained with Pearson's correlation technique were not significant and therefore do not appear again in the text. One-way analysis of variance (ANOVA) or Kruskal-Wallis ANOVA was used to test for differences in numerical variables among more than two groups.

The values of $p<0.05$ were considered statistically significant. All statistical analyses were performed using MedCalc MedCalc Statistical Software version 17.2 (MedCalc Software bvba, Ostend, Belgium).

Results

Overview of patients and therapy

Seventy-three patients (68 women and 5 men, mean age 60±12.5 years) were included in this study. Patient characteristics are shown in Table 2. Forty-eight (65.8%) patients were taking NSAID therapy daily for over a month (irrespective of dose). The median duration of NSAID therapy was 35.4 (IQR 7.3-88.2) months. A single NSAID was used in every case except for one patient who combined two NSAIDs (ketoprofen and diclofenac). Nineteen patients took diclofenac (median daily dose 100 mg, IQR 100-150), 11 took piroxicam (median daily dose 20 mg, IQR 20-20), 6 were on indomethacin (median daily dose 75 mg, IQR 56.3-75), 6 were on ibuprofen (median daily dose 1200 mg, IQR 750-1200), 3 were on ketoprofen (median daily dose 150 mg, IQR 125-175), 1 patient was taking tenoxicam (10 mg daily), 1 was on meloxicam (15 mg daily), and only 1 was on celecoxib (200 mg daily). The relative frequencies of the use of different NSAIDs are shown in Figure 1. NSAIDs were administered either *per os* in 46/48 (95.8%) patients or intrarectally in 2/48 (4.2%) patients. Patients receiving NSAIDs were less frequently taking glucocorticoids ($p=0.026$) (Fig. 2). Glucocorticoid use lasting for a month or longer was noted in 59/73 (80.8%) patients. Glucocorticoids were administered at a median daily dose of 8 (IQR 5-10) mg over a median course of 40.7 (IQR 11.3-82) months. Thirty-nine of 59 (66.1%) patients were taking dexamethasone and 20/59 (33.9%) were taking methylprednisolone. Thirty-five of 73 (47.9%) patients were receiving a combination of NSAID and glucocorticoid therapy daily over a median period of 33.3 (IQR 8.6-74.5) months. Because of the possible implications in the

Table 2. Characteristics of the study group of rheumatoid arthritis patients (overall and divided by presence of NSAID in therapy)

	Overall	NSAID yes	NSAID no	p value
Number of patients	73	48	25	-
Age (years)	60±12.5	59.4±13.2	61.2±11.1	0.569
Gender (female)	68/73 (93.2%)	44/48 (91.7%)	24/25 (96%)	0.655
Duration of RA (years)	IQR (4.3-20)	7.8 IQR (4.4-19)	11 IQR (4.3-21)	0.412
DAS28	6.1 IQR (4.9-6.9)	6.3 IQR (5-7)	6 IQR (4.6-6.7)	0.167
HAQ	2.1 IQR (1.6-2.8)	2.1 IQR (1.6-2.8)	2.1 IQR (1.8-2.5)	0.926
Pain NRS	5.4±1.9	5.7±1.7	5±2.2	0.145
DMARD	37/73 (50.7%)	27/48 (56.3%)	10/25 (40%)	0.188
NSAID	48/73 (65.8%)	-	-	-
GC	59/73 (80.8%)	35/48 (72.9%)	24/25 (96%)	**0.026***
NSAID + GC	35/73 (47.9%)	-	-	-
GI symptoms	17/73 (23.3%)	15/48 (31.3%)	2/25 (8%)	**0.026***
Risk factors for GI side effects	2 IQR (1-2)	2 IQR (1-2)	2 IQR (1-2)	0.190
GI ulcer	12/73 (16.4%)	8/48 (16.7%)	4/25 (16%)	1.000
Anticoagulant therapy	4/73 (5.5%)	2/48 (4.2%)	2/25 (8%)	0.603
Serious systemic disease	6/73 (8.2%)	4/48 (8.3%)	2/25 (8%)	1.000
H. pylori infection	1/73 (1.4%)	1/48 (2.1%)	0/25 (0%)	1.000
Smoking	9/73 (12.3%)	5/48 (10.4%)	4/25 (16%)	0.482
Alcohol	1/73 (1.4%)	1/48 (2.1%)	0/25 (0%)	1.000
ASA	13/73 (17.8%)	9/48 (18.8%)	4/25 (16%)	1.000
High dose or multiple NSAIDs	3/73 (4.1%)	3/48 (6.3%)	0/25 (0%)	0.547
GI risk score	5 IQR (3-6)	4,5 IQR (2.8-6)	5 IQR (3-7)	0.180
PPI in therapy	31/73 (42.5%)	19/48 (39.6%)	12/25 (48%)	0.490

NSAID = non-steroidal anti-inflammatory drugs; RA = rheumatoid arthritis; DAS28 = Disease Activity Score; HAQ = Health Assessment Questionnaire; NRS = Numerical Rating Scale; DMARD = Disease Modifying Antirheumatic Drugs; GC = glucocorticoids; GI = gastrointestinal; *H. pylori* = *Helicobacter pylori*; ASA = acetylsalicylic acid; PPI = proton pump inhibitor; *there was a statistically significant difference in the presence of GC in therapy and presence of GI (χ^2-test, $p<0.05$)

gastrointestinal system, this group was evaluated as a therapeutic group in further analyses.

Only 37/73 (50.7%) patients in our study were taking csDMARDs, either as monotherapy or combined therapy; in the rest of patients, csDMARDs were withdrawn or were not administered because of side effects and contraindications, respectively. The most commonly used csDMARD was methotrexate (27 patients), followed by sulfasalazine (n=23), leflunomide (n=14), chloroquine (n=7) and azathioprine (n=2). At the time of patient inclusion in the study, none of the patients had received bDMARDs. Because of high disease activity, they were hospitalized to evaluate the disease and administer bDMARDs.

Disease activity, pain intensity and functional status

The median value of the DAS28 index was 6.1 (IQR 4.9-6.9). A high level of inflammation (DAS28 ≥5.1) was noted in 50/73 (68.5%) patients. There was no significant difference in the DAS28 index (p=0.167) between patients with and without NSAID therapy and between patients on different therapies (p=0.831), as shown in Figure 3. Patients receiving ASA had a significantly lower DAS28 index (p=0.001) in

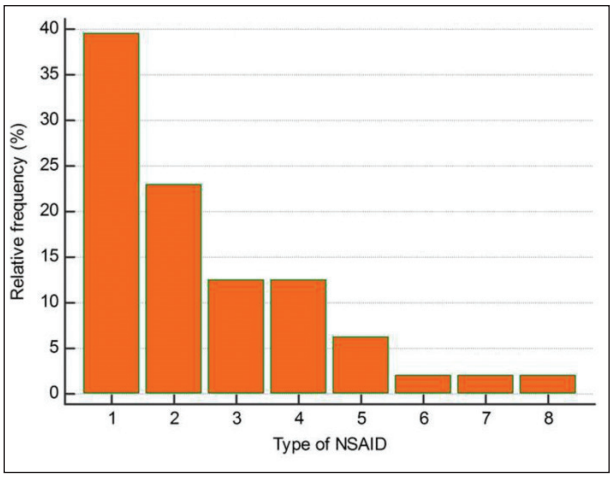

Fig. 1. Use of various non-steroidal anti-inflammatory drugs (NSAIDs) in patients on long-lasting therapy for rheumatoid arthritis; 1 = diclofenac, 2 = piroxicam, 3 = ibuprofen, 4 = indomethacin, 5 = ketoprofen, 6 = tenoxicam, 7 = meloxicam, 8 = celecoxib.

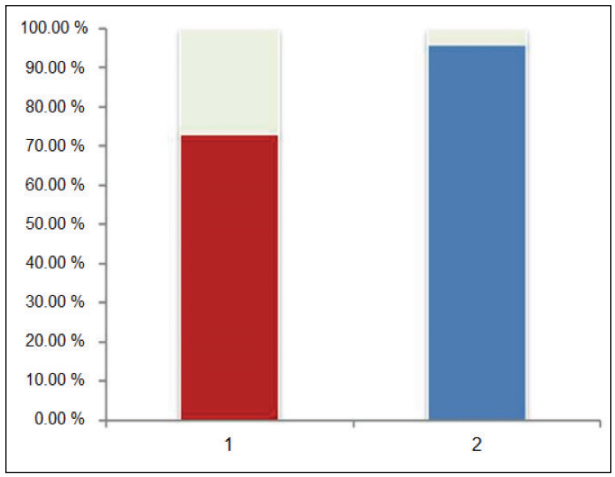

Fig. 2. Patients taking non-steroidal anti-inflammatory drugs (NSAIDs) were less frequently taking glucocorticoids (χ^2-test, p=0.026); 1 = NSAIDs in therapy, 2 = no NSAIDs in therapy.

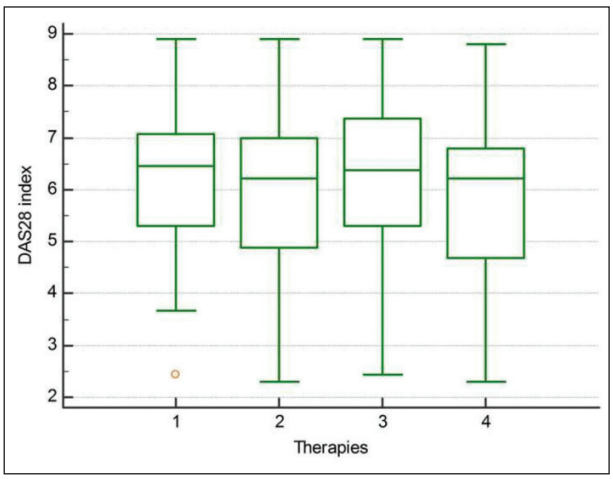

Fig. 3. The Disease Activity Score (DAS28) index did not differ among different treatment groups (Kruskal-Wallis analysis of variance, p=0.831); 1 = non-steroidal anti-inflammatory drugs (NSAIDs), 2 = glucocorticoids (GCs), 3 = NSAID + GC, 4 = disease-modifying anti-rheumatoid drugs.

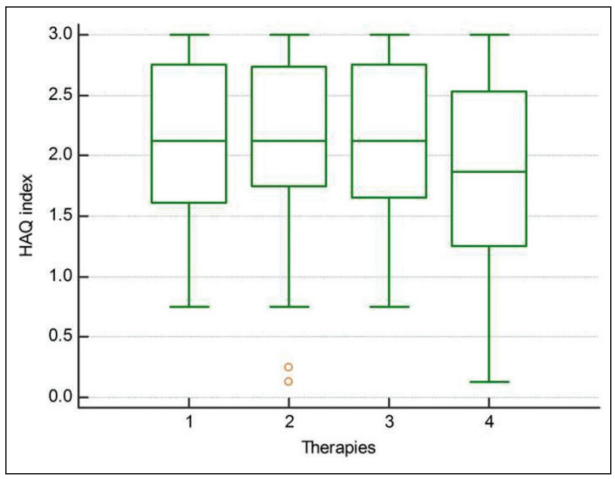

Fig. 4. The Health Assessment Questionnaire (HAQ) index did not differ among different treatment groups (Kruskal-Wallis analysis of variance, p=0.168); 1 = non-steroidal anti-inflammatory drugs (NSAIDs), 2 = glucocorticoids (GCs), 3 = NSAID + GC, 4 = disease-modifying anti-rheumatoid drugs.

comparison to others, probably reflecting the fact that ASA was withheld in most patients that required other forms of therapy because of a high gastrointestinal burden. The DAS28 index was significantly correlated (Spearman) with both the HAQ index (Rho=0.42, p<0.001) and pain intensity (Rho=0.35, p=0.002).

The median value of the HAQ index was 2.1 (IQR 1.6-2.8). The HAQ index did not differ significantly between patients with and without NSAID therapy (p=0.928) and between different treatment groups (p=0.168), as shown in Figure 4. However, patients on DMARD had a significantly lower HAQ

Table 3. Presence of actual gastrointestinal symptoms, particular gastrointestinal risk factors, gastrointestinal risk score and gastroprotection among therapeutic groups

	Overall	NSAIDs	GCs	NSAIDs + GCs	DMARDs	p value
Actual GI symptoms	17/73 (23.3%)	15/48 (31.3%)	15/59 (25.4%)	13/35 (37.1%)	9/37 (24.3%)	0.572
Age >65 years	30/73 (41.1%)	18/48 (37.5%)	25/59 (42.4%)	13/35 (37.1%)	10/37 (27%)	0.509
Positive medical history of ulcer*	12/73 (16.4%)	8/48 (16.7%)	11/59 (18.6%)	7/35 (20%)	6/37 (16.2%)	0.969
Treatment with GC/ NSAID**	35/73 (47.9%)	35/48 (72.9%)	35/59 (59.3%)	35/35 (100%)	17/37 (45.9%)	**<0.001**
High dose of single NSAID or multiple NSAIDs	3/73 (4.1%)	3/48 (6.3%)	2/59 (3.4%)	2/35 (5.7%)	1/37 (2.7%)	0.822
Concomitant ASA in cardioprotective dose	13/73 (17.8%)	9/48 (18.8%)	10/59 (16.9%)	7/35 (20%)	5/37 (13.5%)	0.891
Anticoagulants	4/73 (5.5%)	2/48 (4.2%)	4/59 (6.8%)	2/35 (5.7%)	0/37 (0%)	0.456
Serious comorbidity***	6/73 (8.2%)	4/48 (8.3%)	6/59 (10.2%)	4/35 (11.4%)	2/37 (5.4%)	0.810
H. pylori infection	1/73 (1.4%)	1/48 (2.1%)	1/59 (1.7%)	1/35 (2.9%)	1/37 (2.7%)	0.980
Cigarette smoking	9/73 (12.3%)	5/48 (10.4%)	5/59 (8.5%)	2/35 (5.7%)	7/37 (18.9%)	0.277
Alcohol consumption	1/73 (1.4%)	1/48 (2.1%)	0/59 (0%)	0/35 (0%)	1/37 (2.7%)	0.511
Moderate risk (1 or 2 risk factors)	50/73 (68,5%)	34/48 (70,8%)	40/59 (67,8%)	25/35 (71,4%)	25/37 (67,6%)	0.971
High risk (3 or more risk factors)	12/73 (16.4%)	10/48 (20.8%)	12/59 (20.3%)	10/35 (28.6%)	4/37 (10.8%)	0.312
GI risk score	5 IQR (3 - 6)	4.5 IQR (2.8 - 6)	5 IQR (3 - 7)	5 IQR (3.5 - 7)	3 IQR (2 - 6)	0.052
Gastroprotection****	31/73 (42.5%)	19/48 (39.6%)	28/59 (47.5%)	16/35 (45.7%)	11/37 (29.7%)	0.716

NSAID = non-steroidal anti-inflammatory drugs; GC = glucocorticoids; ASA = acetylsalicylic acid; *H. pylori* = *Helicobacter pylori*; GI = gastrointestinal;
*complicated or uncomplicated; **treatment with GCs in patients on NSAID therapy, or treatment with NSAIDs in patients on GC therapy; ***cardiovascular disease, renal or hepatic insufficiency, uncontrolled diabetes, uncontrolled hypertension; ****proton pump inhibitors were considered for gastroprotective therapy

index when analyzed in comparison with all other patients (p=0.005). The HAQ index was significantly correlated with disease duration (Rho=0.4, p<0.001), gastrointestinal risk score (Rho=0.37, p=0.001), length of NSAID therapy (Rho=0.24, p=0.043), length of glucocorticoid therapy (Rho=0.28, p=0.019), pain intensity (Rho=0.42, p<0.001), and DAS28 index as mentioned previously.

The mean value of pain intensity measured as NRS was 5.4±1.9. NRS did not differ significantly

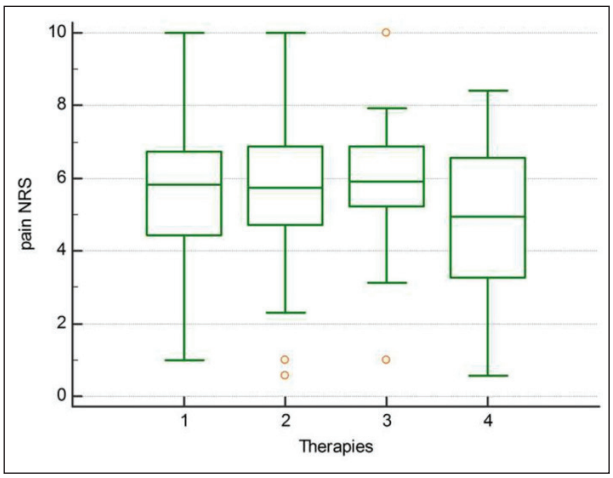

Fig. 5. Pain intensity did not differ among different treatment groups (analysis of variance, p=0.094); 1 = non-steroidal anti-inflammatory drugs (NSAIDs), 2 = glucocorticoids (GCs), 3 = NSAID + GC, 4 = disease-modifying anti-rheumatoid drugs.

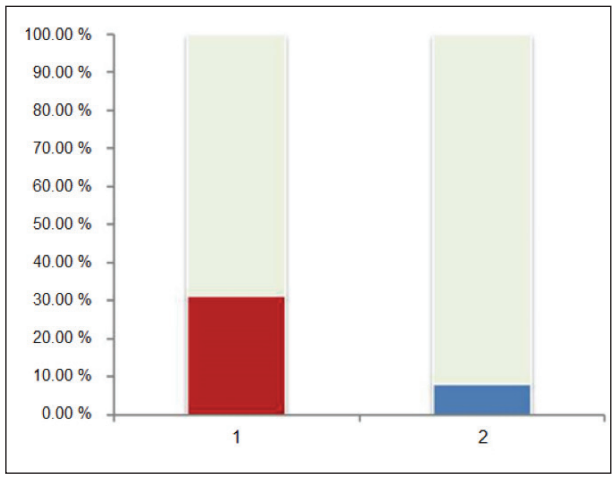

Fig. 6. Presence of gastrointestinal symptoms was more frequent in non-steroidal anti-inflammatory drug (NSAID) users than in non-users (χ2-test, p=0.026); 1 = NSAIDs in therapy, 2 = no NSAIDs in therapy.

between patients with and without NSAID therapy (p=0.145) or between different treatment groups (p=0.094), as shown in Figure 5. However, patients on DMARD had a significantly lower NRS score when compared with other patients (p=0.012). As mentioned previously, the NRS score was significantly correlated with both DAS28 index and HAQ index, as well as with the duration of glucocorticoid therapy (Rho=0.28, p=0.016).

Gastrointestinal symptoms, risk factors for gastrointestinal side effects and gastroprotection

An overview of gastrointestinal symptoms, gastrointestinal risk factors in particular, gastrointestinal risk score, and gastroprotection among therapeutic groups is provided in Table 3. The gastrointestinal symptoms observed in this study were epigastric pain, nausea, vomiting and heartburn. Symptoms occurred periodically throughout the day, although most patients attributed them to their medications. Of 48 patients who were regularly taking NSAIDs, 15 (31.3%) reported that they experienced gastrointestinal symptoms, while 33 (68.8%) patients did not experience any such symptoms. The presence of gastrointestinal symptoms was significantly more frequent among patients continuously using NSAIDs (odds ratio [OR] 5.23, p=0.026) than in non-users, as shown in Figure 6. This also occurred in patients taking NSAID + glucocorticoid (OR 5, p=0.007), but not in patients taking only glucocorticoids (p=0.497) or DMARDs (p=0.832). No correlation was noted between the presence of gastrointestinal symptoms and the duration of NSAID (p=0.073) or glucocorticoid (p=0.734) use. We further evaluated the presence of risk factors for serious gastrointestinal incidents during NSAID treatment. If patients were on NSAID + glucocorticoid therapy, it was considered a single risk factor. In the whole cohort, there was a high prevalence of the aforementioned risk factors; 62 (84.9%) patients on therapy had at least one risk factor, highlighting the possibility of side effects in RA patients and necessitating therapy modification. The percentage of patients with at least one risk factor was even higher, reaching 91.7%, in the group of patients on NSAID therapy. We observed no difference in the presence of particular risk factors between different therapeutic groups, as shown in Table 3, with the exception of the presence of NSAID/glucocorticoid therapy because one of the therapeutic groups was defined by this factor (p>0.05 for all comparisons except for the presence of NSAID/glucocorticoid in therapy). Similarly, the presence of particular risk factors did not differ between patients with and without NSAIDs in therapy (p>0.05 for all comparisons).

We did not observe a statistically significant difference in the gastrointestinal risk score between patients with and without NSAID therapy (p=0.180) or between patients on different therapies (p=0.052). However, because a near-significant effect was observed in the latter case, we report that a significant difference (post-hoc Conover test, p<0.05) was present between patients on DMARD therapy (median 3, IQR 2-6) and patients receiving glucocorticoids (median 5, IQR 3-7) and combined NSAID + glucocorticoid therapy (median 5, IQR 3.3-7). In line with this observation, therapy with DMARDs was significantly associated with a lower gastrointestinal risk score (p=0.03), whereas therapy with glucocorticoids was significantly associated with a higher gastrointestinal risk score (p<0.001) when compared to non-receiving patients.

The number of different risk factors (p=0.139) or gastrointestinal risk score (p=0.460) did not differ between patients with and without gastrointestinal symptoms.

Only proton pump inhibitors were considered to represent gastroprotective therapy, while H2-receptor antagonists were not considered an effective treatment option (used in 3 patients), as verified by the literature[13,17,21,22]. The frequency of patients taking proton pump inhibitors as gastroprotective therapy did not differ between treatment groups (p=0.716) and was not associated with NSAID use (p=0.490), presence of gastrointestinal symptoms (p=0.902), or gastrointestinal risk score (p=0.407).

Discussion

The results of our study demonstrated that NSAIDs were frequently used by patients with active advanced RA, regardless of the DAS28 index, HAQ index, pain intensity, or the presence of risk factors for serious gastrointestinal side effects. Thus, the decision to use NSAIDs is not necessarily dictated by disease activity, degree of functional disability, or pain intensity, nor is their use avoided in patients at a higher risk of gastrointestinal side effects. However, a higher degree of patient functional disability (measured with the HAQ index) required prolonged use in patients taking NSAIDs, identifying functionality in everyday activities as an important factor dictating NSAID use.

In this study, 66% of RA patients with unsatisfactory control of their illness were regular NSAID users, demonstrating how NSAIDs still play a significant role in the treatment of RA, and that treatment is long-lasting despite the availability of other drug classes. Our results also indicate that NSAIDs help exclude glucocorticoid therapy and, therefore, spare patients from the potentially debilitating glucocorticoid-related side effects. NSAIDs are a class of drugs that are self-used by patients and are the only first-line drugs that are prescribed for the most painful stage of RA, especially before a definitive diagnosis has been established. Despite the common use of these drugs, several issues are unclear, such as which type of NSAIDs should be preferentially used in RA and whether NSAIDs should be given continuously or on demand. Our results are in line with the previously published experiences and demonstrate that the most commonly prescribed NSAID is diclofenac, which was being used by nearly 40% of the patients in this study[27]. The doses of diclofenac used in this study were in the range of doses recommended for treating RA signs and symptoms.

In our study population, gastrointestinal symptoms were more common in patients regularly using NSAIDs or NSAID + glucocorticoid combination than in the rest of the population, as expected. Mild gastrointestinal symptoms (epigastric pain, nausea, vomiting, and heartburn) were noted in 31.3% of patients on regular NSAID therapy. Up to 85% of patients on regular NSAID therapy had at least one identifiable risk factor for developing a gastrointestinal incident, 66% had one or two certain risk factors (moderate risk), while 18% had three or more risk factors (high risk). Interestingly, the decision to implement long-lasting NSAID therapy was not influenced by the presence of gastrointestinal risk factors. The most common risk factor for gastrointestinal side effects was the use of glucocorticoids and over 80% of our patients were treated with low doses of glucocorticoids, which could be attributed to the marked disease activity in most patients. Concomitant therapy with NSAIDs and glucocorticoids leads to an increased risk of developing gastrointestinal side effects and this combination is to be avoided whenever possible, particularly in the presence of other gastrointestinal risk factors[28].

Despite the potentially 'dangerous' combination, in this study, no serious gastrointestinal symptoms were observed at the time of hospitalization in these patients. In a study by Singh *et al.*, more than 1900 RA patients were evaluated over a 2.5-year period;

15% of these had some form of gastrointestinal side effects, of which 2.2% required hospitalization due to serious complications. Notably, up to 81% of patients hospitalized due to serious complications reported no prior symptoms[21]. Larkai *et al*. evaluated 65 patients with RA or osteoarthritis on regular NSAID therapy (minimum 6 weeks) by endoscopy. They found mucosal hemorrhages, erosions or both in 44 (68%) patients, while 10 (15.4%) patients had a gastric or duodenal ulcer. Dyspeptic symptoms were present in 3 of 10 patients with a verified peptic ulcer, in 19% of patients who had normal endoscopic findings, and in 9% of patients with abnormal endoscopic findings. The study further showed that gastrointestinal symptoms were a poor indicator of mucosal damage to the stomach or duodenum[29]. Hollenz *et al*. performed a prospective study including 104 patients in the primary healthcare system who were on NSAIDs for a minimum of 2 weeks, predominantly due to back and joint pain. Thirty-five percent of the patients developed dyspeptic symptoms requiring treatment and 16% were diagnosed with a peptic ulcer. The patients who developed an ulcer were unable to be identified on the basis of their symptoms or present risk factors[30].

Many clinical studies investigated the ability of various therapeutic agents to prevent NSAID-induced gastrointestinal side effects. The results of these studies indicated that only proton pump inhibitors were considered for gastroprotective therapy, while H2-receptor antagonists were not considered an effective treatment option[17,21,31,32]. In a study by Garcia *et al*. on the use of gastroprotection in patients with RA and osteoarthritis, gastroprotective therapy was present in 21%-24% of patients and was not dependent on NSAID use[33]. Sturkenboob *et al*. conducted a retrospective study at the primary healthcare level in the Netherlands where they followed NSAID use and presence of various gastrointestinal side effect risk factors among patients. They noted that over 80% of patients with one or more risk factors for a gastrointestinal side effect did not take any gastroprotective medication or COX-2 specific inhibitors[34]. In a study by Francetić *et al*. on the use of gastroprotection in patients on NSAID therapy, the authors found that 66% of patients took proton pump inhibitors or H2 antagonists without having any risk factors warranting their use, while 29% of patients with risk factors did not take any gastroprotective medication[35]. Our observations are in line with these reported findings and suggest that the risk of serious gastrointestinal side effects does not differ between patients with and without gastrointestinal symptoms and that typically, patients have inadequate gastroprotection.

The limitations of this study included a small number of patients, heterogeneous study population according to age and disease stage/duration, and cross-sectional nature of data collection. Furthermore, hospitalized RA patients do not reflect the general RA population. However, in compliance with our country's health and insurance laws, it is not unusual to hospitalize patients with high disease activity. Results from later time points will be needed to further evaluate the effects of long-lasting NSAID therapy.

In summary, this study demonstrated that NSAIDs, which have long been the mainstay of treating RA, are still broadly used although RA treatment options have increased with the advent of DMARDs and biologic drugs. It is necessary to identify patients with risk factors for gastrointestinal side effects, re-evaluate their need for long-lasting NSAID therapy, and prescribe the lowest effective dose for the shortest possible duration. It is important to avoid combining NSAIDs with ulcerogenic medications (glucocorticoids, anticoagulants, salicylates) if possible and in the presence of risk factors, gastroprotective medications should be prescribed because most NSAID-related peptic ulcers are clinically silent.

Key points:

- Non-steroidal anti-inflammatory drugs still have a role to play in the treatment of rheumatoid arthritis.
- The decision to use non-steroidal anti-inflammatory drugs may be independent of disease activity or pain intensity.
- However, their prolonged use seems necessary in patients with greater functional disability.
- Non-steroidal anti-inflammatory drugs enable exclusion of glucocorticoid use, precluding glucocorticoid-associated side effects.

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Sažetak

UPOTREBA NESTEROIDNIH PROTUUPALNIH LIJEKOVA U BOLESNIKA S UZNAPREDOVALIM AKTIVNIM REUMATOIDNIM ARTRITISOM

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Ovo istraživanje imalo je za cilj utvrditi uzimaju li bolesnici s aktivnim reumatoidnim artritisom (RA) redovito nesteroidne protuupalne lijekove (NSAID) i razjasniti ovisi li njihova odluka o uzimanju NSAID-a o aktivnosti bolesti, intenzitetu boli ili funkcionalnom statusu. Istraživanje je također imalo za cilj utvrditi čimbenike rizika za gastrointestinalne nuspojave. Tijekom 6 mjeseci proveli smo presječnu studiju u jednom centru uzastopno hospitaliziranih bolesnika s potvrđenim RA. Svakodnevne životne aktivnosti, intenzitet boli i aktivnost bolesti procijenjeni su upitnikom za procjenu zdravlja, vizualnom analognom ljestvicom, odnosno rezultatom aktivnosti bolesti u 28 zglobova. Od 73 bolesnika s dijagnosticiranim RA njih 48 (66%) redovito je uzimalo NSAID. U usporedbi s ne-korisnicima, korisnici NSAID-a rjeđe su uzimali glukokortikoide. Odluka o primjeni NSAID-a bila je neovisna o aktivnosti bolesti, intenzitetu boli, stupnju funkcionalnog oštećenja ili prisutnosti gastrointestinalnih čimbenika rizika. Međutim, viši stupanj funkcionalnog oštećenja bio je povezan s duljim trajanjem kontinuirane primjene NSAID-a i glukokortikoida. NSAID su još uvijek relevantni za liječenje RA. Na odluku o njihovoj primjeni ne mora nužno utjecati aktivnost bolesti ili intenzitet boli, ali je njihova produljena primjena potrebna u bolesnika s višim stupnjem funkcionalne nesposobnosti. NSAID-i omogućuju isključivanje uporabe glukokortikoida, pošteđujući bolesnika nuspojava povezanih s glukokortikoidima.

Ključne riječi: *Reumatoidni artritis; Nesteroidni protuupalni lijekovi; Gastrointestinalne nuspojave; Glukokortikoidi; Aktivnost bolesti*