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**Original article**

## **Evaluation of Side Effects of Monotherapy and Combined Drug Therapies on Gastrointestinal System in Patients with Juvenile Idiopathic Arthritis**

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### **Abstract**

**Aim:** Juvenile Idiopathic Arthritis (JIA) is the most common rheumatologic disease of childhood. The aim of treatment in children with JIA is to suppress chronic inflammation and chronic joint pain and to provide a normal growth and development.

In our study, we aimed to determine the gastrointestinal side effects of mono-therapy and combined therapy of Disease Modifying Anti-rheumatic Drugs (DMARDs) (methotrexate, sulfasalazine) and corticosteroids.

**Patients and Methods:** Fifty out of 119 patients with JIA, followed-up in our Rheumatology out-patient clinic between the years 1996-2006 were enrolled in the study. The patients were grouped according to duration of drug intake and number of drugs used as; patients receiving therapy  $\leq 3$  years and patients receiving therapy  $> 3$  years; patients treated with one drug and patients treated with multiple drugs. Features of gastrointestinal side effects are evaluated with laboratory and radiological work-up and the difference of side effects between single and combined drug therapies is investigated.

**Results:** Twenty-four (48%) of the cases were female and 26 were male (52%). The average age of the patients was  $11.82 \pm 4.53$  years. There was statistically no significant difference in terms of aminotransferase levels between the patients receiving mono-therapy and combined

therapy and also between the patients that received  $\leq 3$  years and  $> 3$  years therapy.

Prevalence of nausea and vomiting was statistically higher in patients being treated  $>3$  years, in patients receiving  $\geq 2$  drugs and with corticosteroids and methotrexate ( $p=0.0001$ ). There was no significant relation between the type of the drug used and gastrointestinal system bleeding.

**Conclusion:** Combined therapies can be safely used in terms of gastrointestinal side effects under regular follow-up.

**Key words:** Juvenile Idiopathic arthritis, gastrointestinal symptoms, disease-modifying antirheumatic drugs, mono-therapy, combined therapy.

### **Introduction**

Juvenile Idiopathic Arthritis (JIA) is a heterogeneous, idiopathic, chronic inflammatory, rheumatic disease in which immunologic mechanisms thought to play role in the pathogenesis. It is the most common rheumatologic disease of childhood<sup>1</sup>. The aim of treatment in children with JIA is to suppress the chronic inflammation and chronic joint pain and to provide a normal growth and development<sup>2</sup>. With a long term therapy, the destruction in cartilage tissue is decreased, synovitis is controlled and joint deformities are prevented. The treatment of the disease is complicated, there is no totally effective

treatment and the drugs used in treatment have many side effects. Although most of these drugs do not treat the disease but act to suppress the symptoms, prevention of functional loss and improvement of quality of life is provided with this therapy. Since the disease is progressive and can persist in adulthood, long term combined drug therapy may be necessary in some subtypes of the disease<sup>3,4,5</sup>. That is why determination and follow up of side effects of the drugs is important in terms of morbidity and mortality. Duration and dosage of drug therapy, combined therapy, drug interactions and metabolism play an important role in determining the side effect profile<sup>6,7</sup>. Step by step treatment is recently preferred starting with NSAIDs and ending with the DMARDs as needed. Even though the non-steroid anti-inflammatory drugs (NSAIDs) are still the first-line agents in initiation and maintenance therapy, most of the patients need second –line agents and corticosteroids (3). Most of these second-line agents, named Disease-Modifying Anti-rheumatic Drugs (DMARDs), delay the radiological progression of the disease. Among these drugs, methotrexate, sulfasalazine and etanercept are found to be effective in treatment of JIA, as a result of double-blind placebo-controlled studies (4). The choice of treatment depends on the weight of the patient, speed of effectiveness and toxicity. Most commonly preferred drugs are methotrexate and sulfasalazine in this group. Methotrexate, sulfasalazine and corticosteroids among DMARD, have many systemic side effects<sup>4,5,8,9</sup>. Gastrointestinal system (GIS) has great importance in terms of primary side effects and metabolism. In chronic diseases in which long –term therapy is needed, most important factor in determining adjustment to treatment is the type and severity of GIS side effects.

In our study, we aimed to determine the side effects and long-term reliability of mono-therapy and combined therapy of DMARDs (methotrexate, sulfasalazine) -except NSAIDs - and corticosteroids. Features of GIS side effects are evaluated with laboratory and

radiological work-up and the difference of side effects between single and combined drug therapies is investigated.

### Patients and Methods

Fifty out of 119 patients with JIA, followed-up in our Rheumatology out-patient clinic between the years 1996-2006 were investigated retrospectively in the study. The inclusion criteria were; the age at disease onset less than 16, coming to follow-up at 3 months interval at least for 2 years, receiving sulfasalazine, methotrexate or steroid therapy at least one year and receiving at least one of them. None of the patients received NSAID. Patients with systemic JIA that received pulse steroid (30 mg/kg/day) and cases with other chronic disease were excluded from the study. The patients and their families were informed that these data will be used in a study and written informed consents were taken.

ILAR diagnostic criteria were used in grouping the patients (10). Sixteen (32%) of the patients were diagnosed as oligoarticular JIA, 15 (30%) as polyarticular RF(-) JIA, 12 as (24%) systemic onset JIA, 6 as (12%) enthesitis-related arthritis and 1 as (2%) was psoriatic arthritis.

Methotrexate was used as 10-20 mg/m<sup>2</sup>/week, salazopyrine 50 mg/kg/day, methyl prednisolone 0.5-2mg/kg/day in our patients (the preferred dose was ≤ 10mg/day). Steroid therapy was used as a bridge therapy intermittently in patients with systemic JIA, poliarticular JIA and extended oligoarticular JIA. Among these patients,

Full blood count, acute phase reactants, biochemical parameters, PT, aPTT and occult blood in feces were checked in every visit. Together with occult blood in feces, only aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were compared in terms of GIS side effects. AST levels between 20-60 IU/L and ALT levels between 20-40 IU/L were considered as normal. Age, gender, age at onset of the disease, duration of the disease, clinical progress, treatment protocol and duration and GIS side effects

(nausea, vomiting, GIS bleeding, hepatotoxicity) related to treatment were evaluated.

Radiological investigation: The patients treated at least 1 year, were evaluated with ultrasonography method in terms of hepatosteatosis and fibrotic changes in liver. Frequency probe of 7.5 MHz, for children was used.

Demographic analysis: the patients were grouped according to duration of drug usage and number of drugs used as; patients receiving therapy  $\leq 3$  years and patients receiving therapy  $> 3$  years; patients treated with one drug and patients treated with multiple drugs.

Statistical analysis: Graph Pad Prisma V.3 package program was used for evaluation of the statistical data. Definitive statistical methods (mean, standard deviation), t-test for comparison of groups and chi-square test for comparison of qualitative data was used. Results were evaluated at  $p < 0.05$  level.

## Results

The age range of the 50 patients was 3-20 years. Twenty-four (48%) were female and 26 were male (52%). The average age of the patients was  $11.82 \pm 4.53$  years. The average age at onset of the disease was  $7.94 \pm 3.92$  years. There was no statistically significant difference in terms of age between males and females ( $p > 0.05$ ). The height of the patients ranged between 3-10<sup>th</sup> percentile and the weight ranged between 75-90<sup>th</sup> percentile. The age at onset of the disease ranged between 24 months -15 years of age.

When the number of drugs used were considered, 14 patients out of 50 used only 1 out of three drugs (methotrexate, sulfasalazine, corticosteroids) whereas 36 of them used more than 1 drug. When duration of treatment was evaluated, 10 patients had received therapy  $> 3$  years, while 40 patients received therapy  $\leq 3$  years. 32 of the patients (64%) received corticosteroid, 34 (68%) sulfasalazine, and 30

(60%) methotrexate therapy. Mean duration of steroid, sulfasalazine and methotrexate therapies were  $2.5 \pm 2.73$  years (**intermittent-sum of duration of bridge therapies**, 1-16 years),  $2.26 \pm 1.05$  years (1-5 years) and  $2.5 \pm 2$  years (1-10 years intermittently) respectively.

The liver enzyme levels were compared in evaluation of side effects of single and multiple drug therapies on liver. Hepatotoxicity was not seen in any of the patients, and besides AST and ALT levels did not exceed normal values in any of the patients. There was no statistically significant difference in first average AST levels ( $p=0.954$ ) and ALT levels ( $p=0.531$ ) between patients receiving single drug and  $\geq 2$  drugs. There was also no statistically significant difference in last average AST levels ( $p=0.076$ ) and ALT levels ( $p=0.324$ ) between patients receiving single drug and  $\geq 2$  drugs. Even though the last AST and ALT values were higher than the first values; this was not statistically significant because they were still in normal range

The liver enzymes were evaluated to determine effects of drug therapy in patients treated  $> 3$  years. There was no statistically significant difference in terms of first average AST levels ( $p=0.919$ ) and ALT levels ( $p=0.26$ ) between patients treated  $\leq 3$  years and  $> 3$  years. There was also no statistically significant difference in terms of last average AST levels ( $p=0.48$ ) and ALT levels ( $p=0.236$ ) between patients treated  $\leq 3$  years and  $> 3$  years. Although first AST and ALT values of the patients were higher than the last AST and ALT values, this was not statistically significant since they were all in normal range.

Prevalence of nausea and vomiting in patients using  $\geq 2$  drugs was statistically higher than the patients using single drug therapy ( $\chi^2: 8.93$ ,  $p=0.003$ ). There was no statistically significant difference in terms of GIS bleeding in patients using  $\geq 2$  drugs and in patients using single drug therapy ( $\chi^2: 1.15$ ,  $p=0.283$ ) (Table I, see below the references). Similarly, presence of nausea

and vomiting in patients being treated >3 years were statistically higher than the patients being treated ≤3 years ( $\chi^2$ :16.75,  $p$ =0.0001). There was no statistically significant difference between the patients treated ≤3 years and >3 years in terms of GIS bleeding ( $\chi^2$ :0.329,  $p$ =0.566) (Table II, see below the references).

When the drugs that are used were evaluated separately, the prevalence of nausea and vomiting in patients receiving steroid therapy was significantly higher than the patients that did not receive steroid therapy ( $\chi^2$ :6.75,  $p$ =0.009). The prevalence of nausea and vomiting in patients receiving methotrexate therapy was also statistically higher than the patients that did not receive methotrexate ( $\chi^2$ :9.28,  $p$ =0.002). There was no statistically significant difference in terms of nausea and vomiting in treatment with sulfasalazine ( $\chi^2$ :2.59,  $p$ =0.107) (Table III, see below the references).

When the effects of drugs were evaluated separately in terms of prevalence of GIS bleeding, there was no statistically significant difference between the patients receiving steroid therapy and the ones that did not ( $\chi^2$ :1.95,  $p$ =0.162). There was also no statistically significant difference in terms of GIS bleeding prevalence with and without sulfasalazine therapy ( $\chi^2$ :1.69,  $p$ =0.193) and methotrexate therapy ( $\chi^2$ :0.04,  $p$ =0.842) separately.

In liver ultrasonography of 50 patients in our study, none of them had hepatic fibrosis or hepato-steatosis.

## Discussion

Juvenile Idiopathic Arthritis is the most frequently seen rheumatic disease of childhood. The treatment of the disease is complicated, there is no totally effective treatment and the drugs used in treatment have many side effects. Usually multiple drug therapy is needed in controlling the disease. If the clinical picture

is life threatening, new drugs having cytotoxic or biologic effects can be used. Recently, the classical therapy is being changed and more aggressive therapy modalities tend to be preferred in early stages. The consumption of multiple drugs when the disease can not be controlled by a single drug can result in increase in the side effects. The studies on effectiveness and reliability of drugs play an important role in treatment success. The determination of morbidity due to treatment in children with JIA will guide the step by step treatment. Methotrexate, sulfasalazine and corticosteroids, commonly used in JIA, have many side effects on GIS. Methotrexate can cause nausea, vomiting, diarrhea, elevation in liver enzymes and fibrosis of liver in long term therapy<sup>8,11,12</sup>. Sulfasalazine can be hepatotoxic, can lead to diarrhea and is one of the etiologic factors of Macrophage Activation Syndrome (MAS)<sup>13,14</sup>. Corticosteroids can cause drug-related hepato-steatosis and GIS bleeding<sup>2,5,15,16</sup>.

Most of the side effects of drugs are related to pharmacological effects of the drugs and are predictable. Besides this, there can be idiosyncratic reactions that are not related to known pharmacologic effects of the drug, possibly having genetic basis<sup>17</sup>. The idiosyncratic reaction caused by methotrexate leads to activation of liver cells and hepatic fibrosis.<sup>18</sup>

Epidemiological studies on drug side-effects showed that, side-effect profile expands as the number of the drugs used increases due to drug interactions. In our study, when we compared the GIS symptoms due to single and multiple drug therapies, we found out that prevalence of nausea and vomiting was significantly higher in the group receiving multiple drugs. However, there was no statistically significant difference in terms of GIS bleeding distribution. In a study by Lee et al., there were symptoms resembling viral hepatitis like weakness, tiredness, jaundice, loss of

apatite, nausea and vomiting in patients that ended up with hepatotoxicity<sup>18</sup>.

AST and ALT values were evaluated as a marker of hepatotoxicity in our patients. There was no statistically significant difference in terms of first and last AST and ALT values between the patients receiving single drug and combined therapy. Besides this, as number of drugs used increases, in studies on clinical toxicology of drugs; unexpected clinical symptoms, findings and laboratory data as a result of drug interactions can occur. Yokogawa et al in animal experiments reported that in drugs with high hepatotoxic potential, multiple drug regimens were more hepatotoxic. They also found that, AST increment rate in a unit time; maximum values and time taken to return to normal levels were higher than the single drug therapies<sup>19</sup>.

In clinical toxicology studies by Worthley et al when side effects of acute and chronic drug intake were investigated, they found an elevation of time depended side effect profile and this increment was more evident in overdoses in drugs like methotrexate<sup>20</sup>. In cases that the metabolite is responsible for effect or toxicity, slow-metabolizers lead to decrease in drug effect and toxicity. In time-dependant chronic-consumption, frequency of total side effects increase as side effects related to dose dependent over dosage and idiosyncratic reaction frequency increase. In our study, prevalence of nausea and vomiting was significantly higher in patients receiving therapy for more than 3 years whereas there was no statistically significant difference in terms of GIS bleeding (Table II). Likewise, when liver enzymes were evaluated in terms of duration of therapy, we found no statistically significant difference in first and last AST levels between the patients that received treatment  $\leq$  3 years and  $>$  3 years.

In drug related nausea and vomiting, anticancer drugs are the leading group which has central and peripheral effects. Besides

these, many more drugs can cause nausea and vomiting<sup>6</sup>. In our study, when the drugs were evaluated separately, the prevalence of nausea and vomiting was significantly higher in patients receiving corticosteroid and methotrexate therapy (Table III).

When the three drugs were evaluated separately in terms of GIS bleeding, even though no statistically significant relation was found, Nielsen et al in a cohort study on 18.379 patients receiving corticosteroid therapy, reported that corticosteroids alone were not responsible for GIS bleeding but increased the risk in patients using NSAIDs and aspirin and in patients with underlying illness<sup>21</sup>. Wolfe F et al in a 13-year prospective study on 2131 patients with Rheumatoid Arthritis reported that corticosteroid intake was a risk factor for GIS bleeding and this risk increased with consumption of NSAIDs<sup>22</sup>. According to the common results of different studies and sources, corticosteroids are an important risk factor related to dose, time and underlying disease. In our study, even though we did not find a statistically significant relation between steroids and GIS bleeding, since the 3 patients with GIS bleeding in our patient population were all receiving steroids, we think that steroids may have a role in this side effect and still there has to be more extended studies.

In a study by Candelli et al, it is reported that in patients with ulcerative colitis receiving high dose corticosteroid therapy, increment in liver enzymes and hepatosteatosis was detected<sup>23</sup>. In liver ultrasonography of 50 patients in our study, we did not encounter a dose related or idiosyncratically caused hepatic fibrosis due to methotrexate, corticosteroid related steatosis or similar pathologies.

In our patients, we use steroids as a bridge therapy in case of life-threatening systemic symptoms, chronic uveitis treatment and to suppress inflammation rapidly till the effect of the major treatment begins. For this reason, the absence of hepatosteatosis due to

corticosteroids in our patients may be related to short-term and intermittent therapy.

Felson et al, in a meta-analysis on effectiveness and toxicity rates of slow-acting anti-rheumatic drugs, mono-therapy data of methotrexate, sulfasalazine, D-penicillamine and gold salts in patients with rheumatoid arthritis were evaluated. As a result of this meta-analysis, affectivity-toxicity rates were higher in methotrexate therapy and sulfasalazine was found to be less effective<sup>24</sup>. In a double-blind randomized study by Shiroky et al, placebo controlled methotrexate and sulfasalazine combined therapy was monitored in 100 patients with rheumatoid arthritis for 8 years. It is concluded that this combined

therapy was more effective than mono-therapy and similar in terms of toxicity<sup>25</sup>.

In conclusion, in our study there was statistically no difference between mono-therapy and combined therapies in terms of hepatotoxicity and GIS bleeding among our patients with JIA. However, nausea and vomiting was higher in patients receiving combined and long-term therapy. We think that combined therapies can be safely used in terms of gastrointestinal side effects under regular follow-up. However, more detailed studies on larger group of patients that compare the treatment side-effects will be more beneficial.

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**TABLES****Table I:** Gastrointestinal Symptoms in Monotherapy and Combined Drug Therapy.

		Monotherapy		Combined therapy		
		(n)	(%)	(n)	(%)	
<b>Nausea- vomiting</b>	no	13	92.3	16	44.4	$\chi^2:8.93$
	yes	1	7.7	20	55.6	$p=0.003$
<b>GIS bleeding</b>	no	14	100	33	91.7	$\chi^2:1.15$
	yes	0	0	3	8.3	$p=0.283$

$\chi^2$ : Chi-square test

**Table II:** GIS Symptoms in Patients That Received Drug Therapy  $\leq 3$  Years and  $>3$  Years.

		$\leq 3$ years		$>3$ years		
		(n)	(%)	(n)	(%)	
<b>Nausea and vomiting</b>	No	29	71.8	0	0	$\chi^2:16.75$
	Yes	11	28.2	10	100	$p=0.0001$
<b>GIS bleeding</b>	No	38	94.9	9	90	$\chi^2:0.329$
	Yes	2	5.1	1	10	$p=0.566$

$\chi^2$ : Chi-square test.

**Table III:** GIS Symptoms According to Drug Therapy.

		Nausea and vomiting (-)		Nausea and vomiting(+)		
		(n)	(%)	(n)	(%)	
<b>Corticosteroid therapy</b>	No	14	50	3	14.3	$\chi^2:6.75$
	Yes	14	50	18	85.7	$p=0.009$
<b>Sulfasalazine therapy</b>	No	6	21.4	9	42.9	$\chi^2:2.59$
	Yes	22	78.6	12	57.1	$p=0.107$
<b>Methotrexate therapy</b>	No	16	57.1	3	14.3	$\chi^2:9.28$
	Yes	12	42.9	18	85.7	$p=0.002$

$\chi^2$ : Chi-square test.

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