

## First-year purchases of disease-modifying drugs of incident patients with chronic juvenile arthritis in Finland

H. Pohjankoski<sup>1</sup>, K. Latva<sup>2</sup>, H. Kautiainen<sup>3</sup>, H. Säilä<sup>4</sup>, T. Klaukka<sup>5</sup>,  
L. Virta<sup>6</sup>, K. Puolakka<sup>7</sup>, T. Pohjolainen<sup>4</sup>, A. Savolainen<sup>2</sup>

<sup>1</sup>Department of Paediatrics, Päijät-Häme District Central Hospital, Lahti, Finland;

<sup>2</sup>Paediatric Research Centre, Tampere University and University Hospital, Tampere, Finland;

<sup>3</sup>Unit of Family Practice, Central Finland Central Hospital, Jyväskylä, Finland and Unit of Primary Health Care, Kuopio University Hospital, Finland; <sup>4</sup>Orton Rehabilitation Unit, Helsinki, Finland;

<sup>5</sup>Social Insurance Institution of Finland, Research Department, Helsinki, Finland;

<sup>6</sup>Social Insurance Institution of Finland, Research Department, Turku, Finland;

<sup>7</sup>South Karelia Central Hospital, Lappeenranta, Finland.

---

### Abstract

#### Objective

To establish a nationwide overview on drug treatment of juvenile idiopathic arthritis (JIA), which is the most frequent form of chronic arthritis (JA) in children and adolescents. The emphasis is on the first 12 months after diagnosis, and any changes in medication practices during the early years of the present millennium are registered.

---

#### Methods

The Social Insurance Institution (SII) in Finland keeps a national register on individuals granted with a special reimbursement for medication of defined chronic diseases. From that register, we identified by the ICD-code of M08 all JA patients aged 16 years or under with an index day from 2000 through 2007. The prescription register of the SII showed the medication purchased for the patients. The register does not cover infused medications given in hospitals. We evaluated the first disease year's medication and the treatment strategy of the very first three months.

---

#### Results

Within our study period 2000–2007, the proportion of patients using methotrexate during the first year of treatment increased from 54 to 72% ( $p < 0.001$ ). The combination of two or more DMARDs became more popular (increased from 16 to 21%) as the initial treatment strategy. These changes parallel a decrease in per oral glucocorticoids. The proportion of JA patients receiving TNF $\alpha$ -blockers during the first year after diagnose reached the level of about 5% during the years 2004 to 2007.

---

#### Conclusion

The drug treatment of patients with recent onset JA has become more intensive during the course of the new millennium in Finland, a fact expected to improve the disease outcome.

---

#### Key words

juvenile arthritis, medication, methotrexate, glucocorticoids, biologic agents

Heini Pohjankoski, MD  
 Katariina Latva, MD  
 Hannu Kautiainen, BA  
 Hanna Säilä, PhD, MD  
 Timo Klaukka, PhD, MD  
 Lauri Virta, MD  
 Kari Puolakka, PhD, MD  
 Timo Pohjolainen, PhD, MD  
 Anneli Savolainen, PhD, MD

Please address correspondence to:

Dr Heini Pohjankoski,  
 Department of Paediatrics,  
 Keskussairaalankatu 7,  
 15140 Lahti, Finland.  
 E-mail: heini.pohjankoski@phsotey.fi  
 heini.pohjankoski@sci.fi

Received on November 5, 2010; accepted  
 in revised form on April 8, 2011.

© Copyright CLINICAL AND  
 EXPERIMENTAL RHEUMATOLOGY 2011.

## Introduction

Juvenile idiopathic arthritis (JIA) is an autoimmune disease in which a genetic disposition has been recognised (1). The incidence of the disease has been 19.5/100,000 children ( $\leq 16$  years) in Finland (2). JIA has long-standing effects both for the patient and society, so access to a paediatric rheumatologist is of prime importance (3). The earlier the patient is diagnosed and treated, the earlier remission may be attained (4, 5). Due to the largely unknown aetiology of the disease, its pharmaceutical approach has been somewhat experimental and has undergone relevant changes during the decades. In earlier decades, intramuscular gold, glucocorticoids, chloroquine preparations, non-steroidal anti-inflammatory drugs (NSAIDs) (6) and azathioprine was used (7, 8) in Finland until, in the mid-1980s, they were gradually surpassed by methotrexate (MTX) (9). The superiority of MTX became widely evident in 1992 (9), and it quickly gained position as the gold standard for JIA medication. The clinical knowledge of MTX has vastly increased ever since (10). A number of further disease-modifying anti-rheumatic drugs (DMARDs) and biologic agents have been evaluated in JIA (11).

Recent studies recommend early introduction of MTX for maximal effect (5). Patients responding favourably to MTX at six months from disease onset have an improved late outcome (5). Data gained from adult patients with rheumatoid arthritis (RA) show that early aggressive intervention with conventional DMARDs in combination (4) facilitates achieving remission. The same is true for JIA patients (12, 13). Keeping the importance of early treatment in mind, our aim was to evaluate early drug treatment policies in Finland, *i.e.* the drug treatment given immediately after diagnosis during the first three and 12 months, respectively.

## Materials and methods

Finland has a general sickness insurance covering the entire population. By law, drugs prescribed by doctors are partly (42%) reimbursed by Social Insurance Institution (SII). Patients with

certain chronic and severe diseases, such as idiopathic inflammatory rheumatic diseases, are entitled to special (72% or 100%) reimbursement of medication if their condition meets defined criteria. In JA the special reimbursement covers DMARDs and glucocorticoids. To establish entitlement, a doctor's certificate must be filed based on a clinical examination by a paediatric rheumatologist or a fellow in training and describing the proper diagnostic procedures, the ICD-10 diagnosis, and the treatment plan according to good clinical practice. The certificates are checked by a medical examiner physician in the SII before the special reimbursement is granted.

We defined the date of entitlement as the index day. The process in the SII takes a few weeks. Entitlement to new biological agents is granted separately with stringent criteria. Biological agents are not authorised for first line use, but a trial with MTX is required first. The reimbursement decisions are gathered in a register maintained by the SII, as are all reimbursable drugs purchased on a doctor's prescription in the country. From this database we identified the patients aged under 16 years, who from 1 January 2000 to 31 December 2007 for the first time were granted special reimbursement of drugs for treatment of juvenile arthritis. We use JA (ICD10) nomenclature due to the source of data. We included children with the following ICD-10 diagnoses: M08 (prolonged juvenile arthritis) either with (n=458) or without (n=1316) a more specific subcategory, L40.5 psoriatic arthritis (n=33), M45 spondyloarthropathies (n=13) and M46.1 sacroilitis of no obvious other cause (n=6), M05 seropositive (n=24) and M06 seronegative or non-specified rheumatoid arthritis (n=36), and M13.9 non-specified arthritis (n=22). Altogether, 1970 children with chronic juvenile arthritis (JA) (ICD10 M08) were hence identified.

We collected data on prescribed medication purchased by JA (ICD10 M08) patients during 2000–2007. We included purchases made in the 31 days before the index day to include drugs purchased before the entitlement was granted.

Competing interests: none declared.

The rate of introduction of DMARDs, whether single (one DMARD) or combination (two or more DMARDs simultaneously) was our prime interest with special reference to MTX.

Intra-articular and intravenous glucocorticoids and intravenous medications are not included in this study, because these are provided by hospitals without written prescriptions. With the exception of glucocorticoids, intravenous medications are practically never given during the first year. NSAIDs do not belong to the category of specially reimbursed drugs. The use of per oral glucocorticoids was not analysed during the period 2006–7 because of a temporary change in reimbursement of this drug, which could cause bias.

The study plan was approved by the SII before provision of the unidentified data to the study group.

#### Statistical methods

The results are expressed as mean with standard deviation (SD), and measures with a discrete distribution are expressed as counts (%). The most important descriptive values were expressed with 95 percent confidence interval (95%CI). Statistical significance for hypotheses of linearity was evaluated by using the Cochran-Armitage test.

## Results

### Medication

MTX and hydroxychloroquine were the most commonly purchased first-year drugs over the whole study period (Table I). The use of MTX increased significantly ( $p$ -value for linearity  $<0.001$ ) up to 71.5% of patients in 2006–07. The use of hydroxychloroquine decreased, ( $p<0.001$ ) and a declining trend appeared in prednisolone use (Table I). A similar increase appeared during the first three months in MTX in single and combination therapies (Fig. 1).

### Early (3-month) treatment strategy

The most common early treatment strategy was DMARD monotherapy. The number of patients on a single DMARD stayed constant. The number of patients receiving combination therapy increased significantly ( $p<0.001$ ) (Table I).

**Table I.** Medication of chronic juvenile arthritis in the first 3 and 12 months in 2000–2007.

Medication	Years				<i>p</i> -value for linearity
	2000–01 n=449	2002–03 n=477	2004–05 n=515	2006–07 n=529	
<i>Drugs, first 12 months</i>					
Methotrexate	241 (53.7)	321 (67.3)	353 (68.5)	378 (71.5)	<0.001
Hydroxychloroquine	276 (61.5)	288 (60.4)	296 (57.5)	239 (45.2)	<0.001
Prednisolone	127 (28.3)	151 (31.7)	103 (20.0)	NA	
Sulphasalazine	69 (15.4)	68 (14.3)	86 (16.7)	61 (11.5)	0.19
Leflunomide	2 (0.4)	8 (1.7)	5 (1.0)	11 (2.1)	0.08
Gold sodium thiomalate	6 (1.3)	0 (0.0)	0 (0.0)	1 (0.2)	0.01
Auranofin	2 (0.4)	1 (0.2)	1 (0.2)	0 (0.0)	0.18
Azathioprine	3 (0.7)	2 (0.4)	3 (0.6)	4 (0.8)	0.80
Cyclosporine	2 (0.4)	5 (1.0)	2 (0.4)	0 (0.0)	0.14
TNF-inhibitor	0 (0.0)	8 (1.7)	32 (6.2)	25 (4.7)	<0.001
Podophyllotoxin	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0.55
<i>Treatment strategy, first 3 months</i>					
No DMARD or biologic agent	75 (16.7)	84 (17.6)	90 (17.5)	103 (19.5)	0.29
Single therapy	245 (54.6)	236 (49.7)	286 (55.5)	298 (56.3)	0.24
Single therapy with prednisolone	50 (11.1)	45 (9.4)	22 (4.3)	NA	<0.001
Combination* therapy	46 (10.2)	67 (14.0)	83 (16.1)	105 (19.8)	<0.001
Combination therapy with prednisolone	24 (5.3)	33 (6.9)	23 (4.5)	NA	
Prednisolone alone	9 (2.0)	10 (2.1)	7 (1.4)	NA	
TNF-inhibitor** only TNF-inhibitor	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0.37

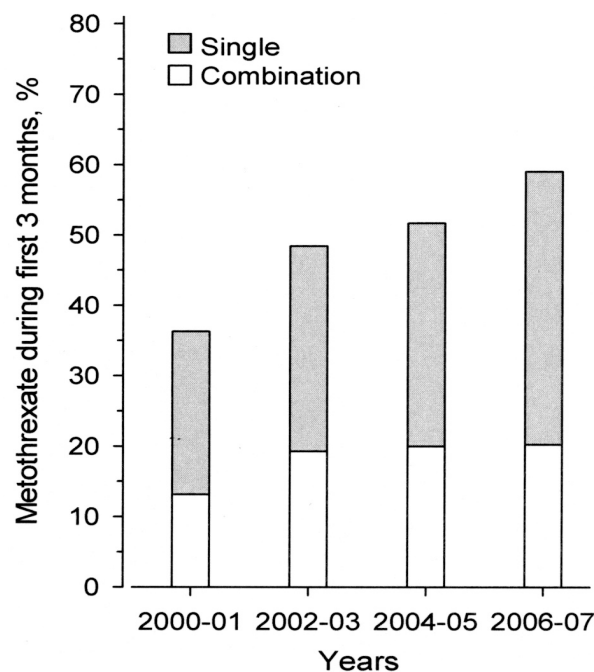
\*Two or more DMARDs; \*\*all TNF-inhibitors as one entity.

Almost a fifth of all patients did not receive a DMARD or a biologic agent during the immediate three months after the date of entitlement. Their number remained constantly below 20 percent over the years.

## Discussion

The present study which covers the entire population of incident JA patients in a country and documents general trends in drug treatment during eight consecutive years is, to our knowledge,

**Fig. 1.** Methotrexate used in combination and single therapies in the three first disease months in patients with JIA during 2000–2007.



the first one of its kind. The most accurate way to examine drug use is observation of the actual intake. Since this is out of reach, examination of purchases rather than prescriptions is the next best method.

The use of MTX increased steadily during both the first 12 and the first 3 months; MTX became the most common drug while glucocorticoid consumption diminished correspondingly. If the first DMARD was not efficient enough, the tendency in the first study years was to add prednisolone to the regime, whereas later, the practice of adding of another DMARD was preferred. The treat to target (TTT) with DMARDs is, besides gaining full remission, the intention to cut down glucocorticoids. Ample evidence shows that the earlier the treatment is started, the better the long-term outcome will be. That is why the urgency of early treatment is emphasised. In the present study we show how early use of MTX may diminish glucocorticoid consumption.

The impact of adult rheumatology and the FIN-RACo study on the treatment strategy can be suggested from our material, reflecting our clinical practice, e.g. the use of sulphasalazine did not decrease, instead, it often became a part of a combination therapy. Hydroxychloroquine was mainly used together with MTX as a combination therapy (14).

Patients with no DMARDs or oral glucocorticoids in the first three months represent almost 20% of all patients. We assume that many of these had mild oligoarthritis or Still's disease treated with NSAIDs and intra-articular glucocorticoids, but compliance problems cannot be excluded. The Finnish way to treat is to inject the inflamed joints with glucocorticoids. The child is then often symptom free the next morning and parents might think it is superfluous to start any other treatment e.g. MTX, and do not purchase it.

There was a limited supply of etaner-

cept in Finland during the first study years. Access to the drug did not improve until summer 2003, which explains the scant use of TNF-inhibitors during 2000–2003.

Among JIA patients, 4.6% have Still's disease in this country (2, 15). From this it might be deduced that 68 patients (~8/year) are missing in our study consisting of only 1% of those with the systemic form of the disease. Their treatment is often started with unreimbursable NSAIDs and glucocorticoids, so no certificate was written.

The ICD-10 diagnoses in certificates are not well in line with the ILAR classification. In an earlier Finnish incidence study on juvenile arthritides, 28 out of 161 cases were found to be chronic, 27/28 fulfilling the American Rheumatology Association criteria for juvenile rheumatoid arthritis (15). Accordingly, we could think that ~70 patients (3.6%; ~9/year) might have their diagnoses revised later (to borreliosis, epiphyseolysis, or the like). Likewise, some JIA patients may have erroneously been given some other diagnosis, but the numbers are surely insignificant.

In summary, we identified major changes in Finnish JA patients' drug treatment in the course of the last decennium. A lengthy follow-up is needed to see whether the patients will benefit from early introduction of DMARDs and from combination therapy, as anticipated.

### Acknowledgements

We would like to thank Mirja Rekola for acquiring the literature.

### References

1. PHELAN JD, THOMPSON SD, GLASS DN: Susceptibility to JRA/JIA: complementing general autoimmune and arthritis trait (review). *Genes Immunol* 2006; 7: 1-10.
2. KAIPIAINEN-SEPPÄNEN O, SAVOLAINEN A: Changes of the incidence of juvenile rheumatoid arthritis in Finland. *Rheumatology* 2001; 40: 928-32.
3. THORNTON J, LUNT M, ASHCROFT DM *et al.*:

Costing juvenile idiopathic arthritis: examining patient-based costs during first year after diagnosis. *Rheumatology* 2008; 47: 985-90.

4. KORPELA M, LAASONEN L, HANNONEN P *et al.*: Retardation of joint damage in patients with early rheumatoid arthritis by initial aggressive treatment with disease-modifying antirheumatic drugs. five year experience from the FIN-RACo study. *Arthritis Rheum* 2004; 50: 2072-81.
5. ALBERS HM, WESSELS JAM, VAN DER STRAATEN RJHM *et al.*: Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. *Arthritis Rheum* 2009; 61: 46-51.
6. IMMONEN K, SAVOLAINEN HA, HAKALA M: Why can we no longer find juvenile idiopathic arthritis-associated amyloidosis in childhood or in adolescence in Finland (letter). *Scand J Rheumatol* 2007; 36: 402-9.
7. SAVOLAINEN HA, KAUTIAINEN H, ISOMÄKI H, AHO K, VERRONEN P: Azathioprine in patients with juvenile chronic arthritis: a long-term follow-up study. *J Rheumatol* 1997; 24: 2444-50.
8. KVIEN TK, HOYERDAL HM, SANDSTAD B: Azathioprine versus placebo in patients with juvenile rheumatoid arthritis: a single center double blind comparative study. *J Rheumatol* 1986; 13: 118-23.
9. GIANNINI EH, BREWER EJ, KUZMINA N *et al.*: Methotrexate in resistant juvenile rheumatoid arthritis. *N Engl J Med* 1992; 326: 1043-9.
10. RUPERTO N, MURRAY KJ, GERLONI V *et al.*: A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004; 50: 2191-201.
11. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78.
12. LOMATER C, GATTINARA M, GERLONI V, ZENI S, FANTINI F: Combination therapy of juvenile rheumatoid arthritis with hydroxychloroquine-gold-methotrexate: a pilot study. *Acta Univ Carol Med (Prague)* 1994; 40: 109-12.
13. RUPERTO N, RAVELLI A, CASTELL E *et al.*: Cyclosporine A in juvenile idiopathic arthritis. Results of the PRCSG/PRINTO phase IV post marketing surveillance study. *Clin Exp Rheumatol* 2006; 24: 599-605.
14. HAAPASAARI J, KAUTIAINEN H, ISOMÄKI H, HAKALA M: Hydroxychloroquine does not decrease serum methotrexate concentrations in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2005; 52: 1621-2.
15. KUNNAMO I, KALLIO P, PELKONEN P: Incidence of arthritis in urban Finnish Children. *Arthritis Rheum* 1986; 29: 1232-8.