Preliminary Results of first Belgian Cohort of Juvenile Idiopathic Arthritis: Where Do we Stand in Terms of Quality of Care and Remission?

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Abstract

Introduction

Juvenile idiopathic arthritis (JIA) represents a very heterogeneous disease. As such, it has been a challenge to describe the disease activity of JIA cohorts. Our objective was to describe the first Belgian cohort of children with JIA by assessing their disease characteristics, outcomes, and potential markers of prognosis.

Methods

The CAP48 cohort is a multicentric observational study of children with recent or well-established diagnosis of JIA (naïve or not to treatment at baseline), evaluated every 3 to 6 months during a follow-up of 10 years.

Results

There were 125 children included, composing of 25 naïve and 100 established patients. Their median age at onset was 6.2 and 4.2 years in the naïve and established cohort respectively, with a predominance of female. All subtypes of JIA were represented in both cohorts. The mean DAS28-CRP and JADAS10-CRP at baseline in naïve patients was 2.52 and 6.0 respectively. Uveitis occurred in 19% of patients and was strongly associated with presence of antinuclear antibodies (odds ratio of 6). Among naïve patients, 55% were in remission at 12 months according to ACR criteria and JADAS10 scores, in contrast with 100% achieving DAS28 remission.

Conclusion

This first cohort study in Belgium allowed to compare its data to other existing cohorts and to evaluate quality of care in Belgian French-speaking hospitals. Additionally, it highlighted a superiority of JADAS10 over DAS28 to monitor and evaluate remission in JIA. This study also underlined a need for more accurate markers of prognosis to improve treatment and long-term outcomes.

Background

Juvenile idiopathic arthritis (JIA) is defined by any form of inflammatory arthritis of unknown cause, with onset in children younger than 16 years and persisting for at least 6 weeks. In literature, its incidence varies between 2-20/100000 in Caucasians and its prevalence between 16-150/100000 children, which is probably underestimated [1, 2]. It represents a very heterogeneous disease and according to the most recent classification by the International League of Associations for Rheumatology (ILAR) in 2001, it can be divided in 7 sub-groups: oligoarthritis (persistent or extended; the latter if > 4 joints are involved after the first 6 months of disease), rheumatoid factor (RF)-positive and -negative polyarthritis, enthesitis-related arthritis (ERA), psoriatic arthritis, systemic arthritis and undifferentiated arthritis [3].
Children can display extra-articular conditions, such as uveitis. As a result, JIA can be associated with a significant morbidity and mortality, depending on its initial presentation and evolution, and represents an important cause of short-term and long-term disability. If left untreated, patients can develop substantial joint destruction with severe orthopedic disabilities, abnormal growth or morphogenesis, or even severe visual impairment if they present concomitant uveitis. Joint erosions impact more frequently patients with a polyarticular course. Uveitis is often asymptomatic at onset and affects predominantly children with oligoarthritis in about 30% of patients; notably, its association with the presence of antinuclear antibody (ANA) has been largely described. Moreover, macrophage activation syndrome, a rare but life-threatening complication of systemic arthritis, can occur in about 5-10% of children within this particular subgroup [1, 2].

Optimal management of the disease may follow a “treat to target” strategy, aiming at clinical remission (or at least minimal disease activity) with the lowest functional impact. It is mainly based on pharmacological treatments, but may also include physical therapy and psychosocial support [4–6]. The use of NSAIDs can represent the first step in treating less-aggressive forms of JIA (mostly oligoarticular forms), and intra-articular injections of steroid can be considered in monoarticular or oligoarticular disease. When more aggressive treatment is needed conventional synthetic DMARDs (csDMARD) and biologic DMARDs (bDMARD) have demonstrated some efficacy with different safety profiles in JIA, while systemic corticosteroids can be used as a short term bridge therapy.

In order to improve management and outcome of patients with JIA, cohort studies are needed to better define characteristics of the disease, specific aspects of individual patients and to reflect on the efficiency of our current medical care.

In this study, we intended to describe the CAP48 cohort, which is the first Belgian cohort of patients with juvenile idiopathic arthritis, including naïve and established patients.

**Methods**

**Study design**

The CAP48 cohort is an observational multicentric study of Belgian children with JIA, followed in Brussels and Wallonia hospitals. In Belgium, most patients with JIA are followed in tertiary centers, as the ones included in our cohort, unless with paucisymptomatic and stable disease. Although fairly representative, not all tertiary centers in the French-speaking part of Belgium have been included in this register.

Patients were included on a voluntary basis at the first visit and followed every 3 months during first year of follow-up, then every 6 months, for a total duration of 2 years at the time of this study (from January 2014 to January 2016) and expected to be followed for a total duration of 10 years. Demographic, clinical, biological and therapeutic data were collected at baseline and at each visit in a standardized form with the referring physician (Fig. 1). The cohort was divided in 2 subgroups: patients with an established disease (already treated with a DMARD) or naïve of any treatment at the time of inclusion.
Only baseline data were collected retrospectively from the medical records in the established cohort, while all other data were collected prospectively according to the described calendar in both naïve and established cohorts.

**Definitions**

The inclusion criterion was a diagnosis of JIA according to the ILAR criteria [3].

The disease activity was followed by both DAS28-CRP and JADAS10-CRP scores. Indeed, at the time of the creation of the CAP48 cohort, the JADAS score was still recent and validated cut-off values had yet to be determined [6–13]. The response to treatment was assessed by pediACR scores and variations of DAS28-CRP values [14], while the clinical remission on and off medication was defined according to the American College of Rheumatology (ACR) criteria revised in 2011 [15] and compared to remission defined according to JADAS10 (JADAS10 ≤1) and DAS28 scores (DAS28 <2.6).

The functional outcome of patients was assessed by the Childhood Health Assessment Questionnaire (CHAQ) [16], with cut-off levels representing no, mild, moderate or severe disability.

The ANA was considered positive for a titer ≥ 1/80, while the RF was evaluated according to the laboratory reference values.

**Statistical analysis**

The statistical analyses were made using SPSS v23.0 (IBM®, Armonk, New York, USA) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA, USA).

The risk of developing uveitis in presence of ANA was evaluated with Fisher’s exact test and odds ratio calculation. The comparisons between remission scores were evaluated with Chi-square Pearson’s tests, followed for significant results by comparisons with Fisher’s exact tests.

Furthermore, the prospective data were submitted to repeated-measures ANOVA tests. Significant results were then followed by Sidak comparison tests (or by Fisher’s least significant difference test if the Sidak test was non-significant). The non-significant results after ANOVA tests were followed by comparisons with Bonferroni correction because of a possible weak power induced by the elimination of incomplete data.

**Results**

**Description of clinical and demographic data at baseline**

One hundred twenty-five patients were enrolled in this study; 100 patients with an established disease and 25 patients considered naïve.
The patients have a median age of 6.2 and 4.2 years at onset in the naïve and established cohort respectively, with a predominance of female (64% and 57% respectively). The distribution of age at onset follows a bimodal distribution, with a first peak between 1 and 4 years and a second peak between 9 and 12 years (Fig. 2).

The symptoms duration before diagnosis is respectively 10.8 and 7.3 months in the naïve and established cohort. A diagnosis delay of $\geq$ 12 months is associated to older age at onset and negativity of ANA. The mean body-mass index (BMI) is around the 75th percentile adjusted for sex and age for both cohorts (Table 1). All forms of JIA are represented in both cohorts, without significant differences between cohorts (Fig. 3).

**Description of treatment among patients at baseline and during follow-up**

In the established cohort, 98% of patients are or have been treated with methotrexate (MTX), while half had been treated with a bDMARD (most of which are still ongoing). Unsurprisingly, the patients most treated with bDMARDs have systemic arthritis, followed by extended form of oligoarthritis, enthesitis-related arthritis, RF-positive and –negative polyarthritis, and persistent form of oligoarthritis, among which respectively 77%, 76%, 73%, 50% and 40% of patients had been treated with bDMARDs.

Among the 25 naïve patients, MTX was started in 44% of patients during the 2 years of follow-up, and 2 children had started a bDMARD.

The details of these treatments are available in Supplementary material.

Approximately one-third of patients (36.8%) reported side effects during follow-up, mainly digestive intolerance (75%), followed by fatigue (11%), headache (7%), allergy at the injection site (4%) and irritability (3%).

**Description of markers of auto-immunity and their relation with clinical characteristics**

Positivity of ANA is found in 40% of naïve patients and 47% of established patients. Interestingly, 19% of patients developed uveitis (all appearing in oligoarthritis forms) and the occurrence of uveitis is strongly associated with the presence of ANA, underlined by an odds ratio of 6 (Table 2). Patients with uveitis are found to be significantly younger at disease onset and diagnosis with a median age of 1.8 and 1.9 years respectively, compared to 7.6 and 9.1 years respectively in unaffected patients (Table 2). In our cohort, they were also mostly female (71%).

HLA-B27 testing was performed on only 35 patients in our cohort. Among these patients, 25% of naïve patients and 37% of established patients are positive for HLA-B27.

**Description of patients’ outcome during the 18 months of follow-up**
Preliminary results from the analysis of the follow-up data show that within the naïve cohort (Fig. 4A), tender joint counts (TJC), C-reactive protein (CRP) and DAS28-CRP are significantly improved at 6 months, while TJC and physician visual analogue scale (VAS) are significantly improved at 12 months of follow-up. Furthermore, out of the 100 established patients (Fig. 4B), 54 had an active disease at baseline. Among them, TJC, swollen joint counts (SJC), physician VAS and DAS28-CRP are significantly improved at 6 months, while TJC, physician VAS and patient/parent VAS are significantly improved at 12 months. In total, 60 to 70% of patients responded to treatment at 6 months (regarding pediACR30), and persisted as long as 18 months. More detailed results are available in Supplementary material.

According to the most stringent definition of remission based on the ACR criteria, the naïve patients are, as expected, significantly more in remission at 12 months and 18 months than at baseline, reaching up to 55% of remission rate at 12 months and 75% at 18 months (Fig. 4C). Of those, 83% are still on medication at 12 months while 17% manage to reach remission off medication, rising to 33% at 18 months. The remission rates are stable among the whole established cohort during the 18 months of follow-up, but are interestingly different when comparing the ACR criteria and DAS28-CRP, while JADAS10 did not differ from the ACR criteria (Fig. 4D).

Globally, higher remission rates are seen in systemic arthritis, RF-negative polyarthritis and persistent forms of oligoarthritis (Fig. 4E-F).

**Determination of clinical and biological markers of prognosis**

The follow-up of naïve patients allows identifying female sex as a predictive marker of response to treatment at 12 months (Table 6). The responders also tend to be older at onset and negative for ANA. The details of these analyses are available in Supplementary material.

No predictive markers of inactivity at 6 months or remission on and off treatment at 12 months could be identified during follow-up.

**Impact on the daily life**

The financial burden for the parents is on average 91€ per month. It includes costs related to physiotherapy, accessories, travel expenses, and medication. Among the 47 patients who completed the specific questionnaires during the follow-up, 5 children benefit from a home care nurse’s visit. Approximately 40% of the children have regular physiotherapy. Around 80% of patients manage to attend gymnastics classes, of which 10% need an adaptation during sports practice. Two thirds of the patients also practice an extracurricular sport.

**Discussion**

The demographic and clinical data of both CAP48 cohorts are globally quite similar to those reported in literature in Caucasians [17–23]. In particular, with an annual incidence of 1.4/100000 children and a prevalence of 14/100000 children, this population falls into the range described in Caucasians, even if
probably underestimated [24]. Indeed, this study based on cohort data overlooks some patients who wouldn’t be missed within the scope of a systematic registry. It is important to note that the clinical characteristics of patients with JIA also depend on geographical and ethnic parameters [25], but the CAP48 cohort comprises mainly Caucasians children (92%). The mean age at onset and diagnosis as well as its distribution are comparable to those observed in the vast Canadian and English naïve cohorts (ReACCH Out and CAPS cohorts) [18, 19]. However, the diagnosis delay is here twice higher, and this difference could be partly explained by ignorance of the disease from parents and general practitioners who wait too long before referring to a specialized center. Moreover, it seems that older age at onset and lack of ANA could be associated with that diagnosis delay. This could be interpreted, especially for the negativity for ANA, by a less severe outcome of the disease.

Curiously, high percentages of HLA-B27 positivity were observed in both cohorts compared to other Caucasian JIA populations [21, 22, 26], without a higher proportion of ERA patients in our cohorts. This can be mostly explained by the fact that only 35 of our patients were tested for HLA-B27 positivity. This non-systematic search is probably guided by the fact that the analysis is not reimbursed for patients, and is therefore essentially performed if the clinical picture can fit within the ILAR classification criteria of the ERA-subtype of JIA (or requires the removal of exclusion criterion b in a boy over 6 years of age at disease onset). The rates found in our cohort are in fact similar to those found in populations of the ERA type [27].

Interestingly, the patients included in this cohort were generally treated in accordance with the last ACR recommendations, with intra-articular corticoids preferentially used in oligoarthritis forms, methotrexate as a first DMARD and biotherapies as a second line of treatment (in the non-systemic forms) [4, 5]. As for the systemic forms, usually more challenging to treat, our data confirm that the patients are essentially treated with systemic corticoids alone (19%), methotrexate monotherapy (12%) or biotherapy in monotherapy or combination therapy (69%). Among these, the most used bDMARDs follow ACR guidelines, with a predominance of IL6 and IL1 inhibitors over TNF inhibitors [28, 29].

The remission rates reach 75% at 18 months in naïve patients and improvement was observed in multiple parameters during follow-up (TJC, SJC, physician VAS, patient/parent VAS, CRP and DAS28-CRP). The comparisons with other cohorts are difficult because of the diversity in population, remission criteria and treatment. Notably, Guzman et al [18] reported a remission rate of 70% within 2 years of follow-up and Nordal et al [21] observed a rate of 51% after 8 years of follow-up. Sengler et al [22] mentioned higher remission rates at 1 year in systemic and oligoarthritis forms, as reported in our study, but our data also found high remission rates in RF-negative polyarthritis forms. Furthermore, it is well known that ACR remission criteria defined by Wallace et al [15] are not systematically used in routine, because of their numerous items to evaluate. We thereby compared the follow-up using DAS28, initially created to monitor patients with rheumatoid arthritis, and JADAS10; our results clearly show better concordance of the remission rates between the ACR criteria and JADAS10, compared to those obtained with DAS28. These results strongly confirm the need to use more systematically the JADAS10 score, created specifically to monitor patients with JIA.
In our study, a good response to treatment is associated with female sex. No other prognosis factors could be identified, probably because of a small cohort size. However, we confirm the higher risk of developing uveitis if the patient is younger at disease onset or diagnosis, or in presence of ANA, as described in prior publications [30–32].

The CAP48 cohort was also designed to evaluate the impact of the disease on patients’ daily life and its physical burden. Many patients obviously need regular physiotherapy, but we observe in our cohort that most patients do not suffer from too great a physical handicap and, for example, are able to attend school gym classes without any specific accommodations or practice an extracurricular sport. Still, we should keep in mind that there is always room for improvement in the management of our patients.

Finally, our study obviously presents some limitations. Our cohort is limited in the number of patients included, especially those with an early diagnosis. The established cohort provides important information concerning disease activity and progression, but its interpretation can be limited by the random moment in disease course at inclusion. Furthermore, as the CAP48 cohort is a cohort that includes new patients on an ongoing basis, the prospective follow-up data presented in this study are still preliminary and will require a more comprehensive study at a later date. The patients included were followed in specialized centers and this could therefore constitute a selection bias by the gathering of potentially more severe patients necessitating more intensive treatment. Moreover, the JIA population is very heterogeneous and leads to analysis in subgroups.

In conclusion, this first cohort study in Belgium permitted to review the distinctive features of the disease. It also allowed to compare epidemiologic and clinical data to other existing cohorts, and to evaluate quality of care in our French-speaking hospitals. Additionally, it highlighted a clear benefit of using JADAS10 to monitor and evaluate remission in JIA, rather than using DAS28, and the necessity to systematically collect some clinical parameters in routine (such as the CHAQ and the patient/parent VAS).

**Abbreviations**

ACR: American College of Rheumatology

ANA: antinuclear antibodies

BMI: mean body-mass index

CHAQ: childhood health assessment questionnaire

CRP: C-reactive protein

ERA: enthesitis-related arthritis

ILAR: International League of Associations for Rheumatology
JIA: juvenile idiopathic arthritis
MTX: methotrexate
RF: rheumatoid factor
TJC: tender joint counts
SJC: swollen joint counts
VAS: visual analogue scale

Declarations

Ethics

This study complies with the Declaration of Helsinki and was approved by the ethics comities of each hospital involved. Informed consent has been obtained from each patient and parents.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

All authors made substantial contributions to the acquisition of data. All authors read and approved the final manuscript.

Acknowledgements

Investigators of the CAP48 cohort: Jean-Pierre Brasseur¹, Benoït Brasseur² and David Tuerlinckx².
References


**Tables**

**Table 1.**
## Table 1. Demographics and baseline characteristics in the two JIA cohorts.

JIA, juvenile idiopathic arthritis; BMI, body mass index; RF, rheumatoid factor.

<table>
<thead>
<tr>
<th>Description</th>
<th>Naives JIA (n=25)</th>
<th>Established JIA (n=100)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>16 (64)</td>
<td>57 (57)</td>
<td>0.65</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>18.3 (1.0)</td>
<td>18.7 (0.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>JIA category</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>3 (12)</td>
<td>13 (13)</td>
<td>1</td>
</tr>
<tr>
<td>Oligoarthritis</td>
<td>17 (68)</td>
<td>60 (60)</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Persistent</strong></td>
<td>1 (6)</td>
<td>17 (28)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Extended</strong></td>
<td>1 (4)</td>
<td>15 (15)</td>
<td>0.19</td>
</tr>
<tr>
<td>Polyaarthritis</td>
<td>0 (0)</td>
<td>11 (73)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>RF+</strong></td>
<td>3 (12)</td>
<td>11 (11)</td>
<td>1</td>
</tr>
<tr>
<td><strong>RF-</strong></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Psoriasic arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enthesitis-associated arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at inclusion, years</td>
<td>11.9 (1.7-16.8)</td>
<td>12.3 (2.6-18.3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Age at first symptoms, years</td>
<td>6.2 (1.1-15.8)</td>
<td>4.2 (0.5-16.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>9.1 (1.4-16.7)</td>
<td>5.0 (0.5-17.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Diagnosis delay, months</td>
<td>10.8 (3.3)</td>
<td>7.3 (1.3)</td>
<td>0.25</td>
</tr>
<tr>
<td>Age at start of long-term treatment, years</td>
<td>9.8 (1.7-16.8)</td>
<td>6.3 (0.8-17.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Therapeutic delay, months</td>
<td>8.9 (4.5)</td>
<td>9.1 (2.1)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

## Table 2.

<table>
<thead>
<tr>
<th>Description</th>
<th>Uveitis (n=24)</th>
<th>No uveitis (n=101)</th>
<th>p-value</th>
<th>OR (CI 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA+ n (%)</td>
<td>19 (79.2)</td>
<td>38 (37.6)</td>
<td>0.0004</td>
<td>6.3 (2.2-18.3)</td>
</tr>
<tr>
<td>Age at disease onset, years</td>
<td>1.8 (0.5-15.2)</td>
<td>7.6 (0.6-16.7)</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>1.9 (0.5-15.2)</td>
<td>9.1 (0.7-17.9)</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2. Risk of developing uveitis according to positivity for antinuclear antibodies and age at disease onset and diagnosis. ANA, antinuclear antibody.

Figures

**BASELINE VISIT**

**Demographic data**

**Clinical data**
- Disease chronology, history of uveitis or systemic disease, personal or familial medical history, ...

**Biologic data**
- ANA/RF/ACPA, HLA B27 typing
- Initial blood test

**Routine consultation**
- Weight, height, TJC, SJC, presence of: uveitis, infection, systemic disease
- Scores: parent/patient VAS, physician VAS, CHAQ, DAS28, JADAS10
- Ongoing treatment and pediACR
- Blood test (incl. CRP and/or ESR)

**EVERY 3 MONTHS during 1st year**
**Then: EVERY 6 MONTHS**

**Routine consultation**
- Weight, height, TJC, SJC, presence of: uveitis, infection, systemic disease
- Scores: parent/patient VAS, physician VAS, CHAQ, DAS28, JADAS10
- Ongoing treatment and pediACR
- Blood test (incl. CRP and/or ESR)

**Figure 1**

Description of visits timeline among the CAP48 cohort and data collection. ANA, antinuclear antibodies; RF, rheumatoid factor; ACPA, anti-citrullinated protein antibodies; TJC, tender joint count; SJC, swollen joint count; VAS, disease evaluation by visual analogue scale; CHAQ, Childhood Health Assessment Questionnaire; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.
Figure 2

Distribution of age (in years) at disease onset, in naive (A) and established (B) patients.

Figure 3

Distribution of juvenile idiopathic arthritis categories in naïve (A) and established (B) patients. P, persistent; E, extended; RF, rheumatoid factor; ERA, enthesitis-related arthritis.
Figure 4

Patients’ outcome during 18 months of follow-up. (A-B) Evolution of parameters among naïve patients (A) and established patients active at baseline (B). (C-D) Remission rates among naïve (C) and established patients (D), according to different remission criteria. (E-F) Remission rates according to JIA categories, among established patients at baseline (n = 100) (E) and at 12 months among the group composed of established JIA active at baseline (n = 54) and naïve JIA (n = 25) (F). TJC, tender joint count; VAS, disease evaluation on a visual analogue scale; CRP, C-reactive protein; SJC, swollen joint count; RF, rheumatoid factor; *, p<0.05; **, p<0.01; ***, p<0.001; ****, p<0.0001.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalTableA1.docx
- AdditionalTableA2.docx
- AdditionalTableA3.docx
- AdditionalTableA4.docx