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

Background

Juvenile idiopathic arthritis (JIA) represents a very heterogeneous disease, and our objectives were to describe the first Belgian cohort of children with JIA, assess their disease characteristics and outcome and identify potential markers of prognosis.

Methods

The CAP48 cohort is a multicentric observational study of children with a recent or well-established diagnosis of JIA (naïve or not to treatment at baseline), evaluated every 6 months during a follow-up of 5 to 10 years.

Results

There were 125 children included in the cohort, composed of 25 naïve and 100 established patients. The patients had a median age of 6.2 and 4.2 years at onset 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). Fifty-five percent of naïve patients were in remission at 12 months of follow-up according to the 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 various extra-articular conditions, such as inflammatory bowel disease and 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 (1, 2).

Management of the disease follows a “treat to target” strategy, aiming at remission with the lowest functional impact. It combines physical therapy, as well as psychosocial support and pharmacological treatment. The use of NSAIDs remain mostly the first step in treating JIA, and intra-articular injections of steroid can be considered in monoarticular or oligoarticular disease. When more aggressive treatment is needed, systemic corticosteroid, conventional synthetic DMARDs (csDMARD) and biologic DMARDs (bDMARD) have demonstrated some efficacy with different safety profiles in JIA.

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. The patients were 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. Demographic, clinical, biological and therapeutic data were collected at baseline and at each visit (Fig. 1). The cohort was divided in 2 subgroups: patients with an established disease (already treated with a DMARD) or naive of any treatment at the time of inclusion.

**Definitions**

The inclusion criterion was a diagnosis of JIA according to the ILAR criteria (3).

The disease activity was followed by DAS28-CRP and JADAS10-CRP scores (scores most used in routine) (4, 5). The response to treatment was assessed by pediACR scores and variations of DAS28-CRP values.
(6), while the disease inactivity was defined according to the American College of Rheumatology (ACR) criteria revised in 2011 (7).

The functional outcome of patients was assessed by the Childhood Health Assessment Questionnaire (CHAQ) (8), with cut-off levels representing no, mild, moderate or severe disability.

The ANA was considered positive for a titer $\geq 1/160$, 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 exact 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).
Table 1

Demographics and baseline characteristics in the two JIA cohorts. JIA, juvenile idiopathic arthritis; BMI, body mass index; RF, rheumatoid factor.

|                                | Naives JIA (n = 25) | Established JIA (n = 100) |
|--------------------------------|---------------------|---------------------------|
| **Female sex**                 | 16 (64)             | 57 (57)                   |
| **BMI, kg/m²**                 | 18.3 (1.0)          | 18.7 (0.4)                |
| **JIA category**               |                     |                           |
| Systemic                       | 3 (12)              | 13 (13)                   |
| Oligoarthritis                 | 1 (6)               | 17 (28)                   |
| - *Persistent*                 | 1 (4)               | 15 (15)                   |
| - *Extended*                   | 1 (100)             | 4 (27)                    |
| Polyarthritis                  | 0 (0)               | 11 (73)                   |
| - *RF+*                        | 1 (4)               | 1 (1)                     |
| - *RF-*                        | 3 (12)              | 11 (11)                   |
| Psoriasic arthritis            | 0 (0)               | 0 (0)                     |
| Enthesitis-associated arthritis|                     |                           |
| Undetermined                   |                     |                           |
| **Age at inclusion, years**    | 11.9 (1.7–16.8)     | 12.3 (2.6–18.3)           |
| **Age at first symptoms, years**| 6.2 (1.1–15.8)    | 4.2 (0.5–16.7)            |
| **Age at diagnosis, years**    | 9.1 (1.4–16.7)      | 5.0 (0.5–17.9)            |
| **Diagnosis delay, months**    | 10.8 (3.3)          | 7.3 (1.3)                 |
| **Age at start of long-term treatment, years** | 13.3 (5.2–16.8) | 6.3 (0.8–17.4) |
|                         | Naives JIA (n = 25) | Established JIA (n = 100) |
|-------------------------|---------------------|---------------------------|
| Therapeutic delay, months mean (SEM) | 14.3 (5.7)          | 9.1 (2.1)                |

**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.

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

Twenty-five percent of naïve patients and 37% of established patients are positive for HLA-B27, while 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).

| Risk of developing uveitis according to positivity for antinuclear antibodies. ANA, antinuclear antibody. | Uveitis in patients ANA+ | Uveitis in patients ANA- | p-value | OR (CI 95%) |
|--------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|---------|-------------|
| Seropositive status defined by at least one ANA+ n (%)                                                  | 19 (79)                  | 5 (21)                   | 0.0004  | 6.3 (2.2–18.3) |
| Seropositive status defined by at least two ANA+ n (%)                                                  | 14 (58)                  | 10 (42)                  | 0.0005  | 5.7 (2.2–14.6) |
Description of patients’ outcome during the 18 months of follow-up

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, 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). 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 at 12 months could be identified during follow-up.

Discussion

The demographic and clinical data of both CAP48 cohorts are globally quite similar to those reported in literature in Caucasians (9–15). 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 (16). 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 (17), 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) (10, 11). 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.

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) (18, 19). 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 (19).

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 (10) reported a remission rate of 70% within 2 years of follow-up and Nordal et al (13) observed a rate of 51% after 8 years of follow-up. Sengler et al (14) 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 (7) 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 study and develop even further this 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 in presence of ANA, as described (20, 21).

Finally, our study obviously presents some limitations. Our cohort is limited in the number of patients included, especially those with an early diagnosis. 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 AJI 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).

This study was approved by ethic comities of each hospital involved. Informed consent was obtained from each patient and parents.

**Abbreviations**

ACR
American College of Rheumatology

ANA
antinuclear antibodies

BMI
mean body-mass index

CHACHildhood 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

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