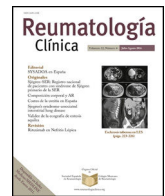




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Original article

Real life treatment in juvenile idiopathic arthritis: Is remission long lasting?



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ABSTRACT

Objectives: Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease that can cause pediatric disability. Achieving stable remission is the main objective to avoid disability. We evaluated remission survival in a cohort of patients with JIA and analyzed factors that might influence long lasting remission.

Methods: We designed an observational, retrospective and longitudinal study of JIA patients. Remission survival was determined from the first visit in clinical remission to the first flare after remission or the last visit recorded at the end of the study. Stable remission was defined as patients fulfilling the Wallace criteria during 18 months of the Covid pandemic. To compare the role of treatment on stable remission, we divided patients into three groups: without systemic treatment, treated with methotrexate only and treated with biologics.

Results: We included 82 JIA patients, 68.3% of whom were female and the median age of disease onset was 4.49 years old. There were no differences in the remission survival rates between JIA subgroups. Nearly 80% had maintained remission at 3 years and a high proportion of patients (68.3%) were still in remission after 5 years. Fifty-seven patients (69.5%) reached stable remission throughout 18 months of the Covid-19 pandemic. Stable remission was more likely in patients without systemic treatment (47.4%) ($p = 0.015$).

Conclusions: Remission survival was long-term in real life conditions, with nearly 80% of our patients maintaining stable remission after 3 years. Flares were more frequent in patients treated with methotrexate in monotherapy.

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Tratamiento en práctica clínica habitual en la artritis idiopática juvenil. ¿Es la remisión duradera?

RESUMEN

Objetivos: La artritis idiopática juvenil (AIJ) es una enfermedad crónica inflamatoria que puede generar discapacidad en pacientes pediátricos. Lograr una remisión estable es el principal objetivo para evitarlo. Evaluamos la supervivencia de la remisión en una cohorte de pacientes con AIJ y analizamos los factores que podrían influir en la remisión duradera.

Métodos: Se diseñó un estudio observacional, retrospectivo y longitudinal de pacientes con AIJ. La supervivencia de la remisión se determinó desde la primera visita en remisión clínica hasta el primer brote después de la remisión o la última visita registrada al final del estudio. La remisión estable se definió como los pacientes que cumplieron los criterios de Wallace durante los 18 meses de la pandemia de covid-19. Comparamos la remisión estable según el tratamiento recibido: sin tratamiento sistémico, tratados solo con metotrexato y tratados con fármacos biológicos.

Palabras clave:

Artritis idiopática juvenil

Remisión

Tratamiento sistémico

Metotrexato

Abbreviations: JIA, juvenile idiopathic arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; DMARDs, synthetic disease-modifying anti-rheumatic drugs; RF, rheumatoid factor; ACPA, anti-citrullinated peptide antibodies; ANA, antinuclear antibodies; HR, hazard ratio.

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Resultados: Se incluyeron 82 pacientes con AIJ. El 68,3% eran mujeres, y la mediana de edad de inicio de la enfermedad fue de 4,49 años. No hubo diferencias en las tasas de supervivencia de la remisión entre los subgrupos de AIJ. Casi el 80% había mantenido la remisión a los 3 años y un alto porcentaje de pacientes (68,3%) seguían en remisión a los 5 años. El 69,5% alcanzó una remisión estable a lo largo de los 18 meses de pandemia de covid-19. La remisión estable fue más probable en los pacientes sin tratamiento sistémico (47,4%) ($p = 0,015$).

Conclusiones: La supervivencia de la remisión fue duradera con casi el 80% de nuestros pacientes, manteniendo una remisión estable después de 3 años. Los brotes fueron más frecuentes en los pacientes tratados con metotrexato en monoterapia.

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Background

Juvenile idiopathic arthritis (JIA) is a heterogeneous disease defined as arthritis lasting longer than 6 weeks in patients under 16 years old.¹ JIA can be a significant cause of pediatric disability and quality of life impairment, extending well into adulthood.² Chronic inflammatory flares can cause chronic joint and ocular damage, reducing physical function and causing further detriment. In order to avoid such outcomes, a rheumatologist's objective is to achieve complete disease remission, maintaining it as long as possible. JIA remission is defined by the Wallace criteria as the absence of any inflammation including that which might affect the joints, periarticular tissues, as well as ocular and systemic inflammation.³

The pharmacological approach to JIA includes the following: non-steroidal anti-inflammatory drugs (NSAIDs); steroids; synthetic disease-modifying anti-rheumatic drugs (DMARDs), mainly methotrexate; and biological DMARDs, starting with tumor necrosis factor inhibitors.^{4,5} In cases where there is only one or two joints affected, intra-articular corticosteroids, especially triamcinolone hexacetonide, are also a good option to control acute inflammation.⁶ DMARDs have demonstrated a high efficacy and a favorable safety profile in JIA, achieving in many cases a complete remission within a few months.⁷

The treat-to-target strategy is quite important to achieve remission.⁸ Many patients start the disease at a very young age with a non-ossified skeleton. Therefore, as soon as we can control disease the better to avoid damage in the future. The treatment received and the JIA subtype are also factors that can have a significant impact on the likelihood of maintaining stable remission. The clinical course can vary among JIA subtypes, as do treatment responses. Moreover, efficacy of treatment also seems to depend on the type of medication used, the adherence to the treatment and the time it was initiated, with early onset being a key aspect of treatment strategies.^{9–11}

In recent years numerous studies have reported on remission in JIA patients and the factors that influence it, not only in cross-sectional studies, but also in prospective observational studies.^{12–14} When and how treatment is started can influence remission rates. However, specific guidelines which to assist clinicians are still lacking; thus predicting outcomes in daily clinical practice remains challenging.

The objectives of our study were to evaluate clinical remission in a cohort of patients with JIA, how long the remission lasted, and which factors might influence either remission or relapse.

Materials and methods

We designed a single-center, observational, retrospective and longitudinal study. We included all patients diagnosed with JIA and that they had at least one follow-up visit during the period from January 2020 to July 2021. We excluded patients who lost to follow-up (i.e., who failed to have at any visits for more than one year).

Demographic and clinical variables were collected (current age and ages at disease onset and disease diagnosis, sex, JIA subcategory, any history of uveitis, autoantibodies (rheumatoid factor (RF), Anti-citrullinated peptide antibodies (ACPA), antinuclear antibodies (ANA)), HLA-B27 and date of first visit with clinical remission). We also recorded all current and past treatments administered to each patient.

Inflammatory flares were documented including uveitis, articular inflammation and systemic symptoms related to JIA. Any treatment changes required at any point during the study were also collected. All methods were carried out in accordance with relevant guidelines and regulations (STROBE guidelines).¹⁵

Definitions

JIA subgroups. As our cohort was small, we divided the patient into four groups based on the clinical course and pathophysiology. Group 1 consisted of patients with persistent oligoarticular JIA. Group 2 was comprised of patients who underwent a polyarticular treatment course, including extended oligoarticular JIA and both RF negative and positive polyarticular JIA. Group 3 were those patients with juvenile spondyloarthritis, including enthesitis related to arthritis and psoriatic JIA. The last group were classified as systemic JIA.

Systemic treatments included immunomodulatory drugs such as systemic steroids, as well as synthetic and biological DMARDs (including Janus Kinase inhibitors). NSAIDs were considered a symptom-relief treatment and were not included in the systemic treatment category.

Clinical remission of the disease was defined as no inflammatory signs in any target organ on/off treatment: e.g., no active joints, no fever, no rash, no serositis, no splenomegaly or lymphadenopathy attributable to JIA; and neither active uveitis nor raised acute phase reactants.³

A clinical flare was defined as any inflammation (fever, rash, organomegaly or adenopathy, arthritis, tenosynovitis or uveitis) related to JIA and confirmed by a physician. We also considered the patient as "flaring" when treatment was increased or added during consultation (i.e., oral or intraarticular steroids, synthetic or biological DMARDs).

Stable remission was defined as patients in clinical remission, previously defined, at every single follow-up visit over 18 months, from January 2020 to July 2021, without any inflammatory flares between visits and without any systemic treatment increase or intraarticular injection. We selected this period because it had been more difficult to attend JIA patients due to the SARS-CoV-2 pandemic and it better reflects changes vis-à-vis the usual remission status. We have also calculated the percentage of patients who had maintained stable remission according to Wallace's criteria for 12 months prior to the study period.

We calculated remission survival using the Kaplan Meier curve for all patients from the first visit in clinical remission (no clinical

cal activity) to the first relapse of any kind (systemic, articular or ocular) or the last visit available.

Analysis of stable remission by group

We divided our cohort into three groups according to the treatment received:

The first group consisted of patients “without systemic treatment”. This group included patients who never received systemic treatment or those who had received systemic treatment in the past, but it was discontinued due to disease inactivity before January 2020.³

The second group was comprised of patients treated with a “Synthetic DMARD”, mainly patients who received methotrexate.

Finally, the third group contained the patients treated with a “biological treatment”, including both monotherapy and in combination with methotrexate. We compared the characteristics of each group and whether or not stable remission differed between them.

We also compared patients who experienced a flare during the 18-month period to those who maintained remission.

Statistical analysis

Nominal variables are expressed in percentages and absolute values. The level of statistical significance was set to 0.05. To compare nominal variables, we used Pearson Chi-square and Fisher's tests χ^2 . A *t*-test and ANOVA test were used to compare remission and quantitative variables. For the multivariate analysis, logistic and lineal regression models were used. Remission survival rates are expressed using Kaplan–Meier curves.

Results

We included a total of 87 JIA patients, 56 (68.3%) of whom were females, and the median age 12.1 (9.1–15.7) years. There were 6 patients with less than 1 year from disease onset and 5 patients that were lost to follow-up.

At the beginning of the study (January 2020), 31 patients (37.8%) had received no systemic treatment for at least 1 year before, and only 6 (7.3%) had never received any systemic treatment. 8 out of those 31 patients had been administered biologic DMARDs with or without methotrexate and 25 had received methotrexate only. There were 17 patients out of the total (20.73%) who were on methotrexate (8 of them had received biological therapy in the past) and 34 patients (41.46%) were on biological therapy, either monotherapy or in combination with methotrexate. The median time to start methotrexate after a JIA diagnosis was 4.56 months and to start biological therapy was 18.72 months. None of the patients were taking NSAIDs as a chronic treatment. The demographic characteristics are shown in [Table 1](#).

Stable remission during the Covid-19 pandemic was more likely in patients without any treatment than in those who received either methotrexate or biologic therapies ($p=0.003$). During the 18-month follow-up, only patients who received methotrexate therapy seemed to have a higher risk of flares ($p=0.02$).

Polyarticular course JIA was the only group in our cohort that was statistically more likely to be classified in the biologic group ($p=0.01$). There were no differences between the remaining JIA subgroups and the treatment received.

Remission survival in clinical practice

Clinical remission was maintained in a high percentage of patients after one year (92.5%), after three years (78.5%) and was even maintained in a large proportion of patients after five years (68.3%). [Fig. 1](#) shows the remission survival curves of our cohort.

All remission survival curves seemed to stabilize after 4 years of follow-up, without any flares thereafter.

Patients with stable remission for 3 years or longer

There were 44 patients (78.5%) whom maintained remission during at least 36 months; 27 were females (61.36%), with a median age at disease onset of 53.8 months (29.76–93.84). The JIA subcategories of this group were 23 oligoarticular (52.27%), 9 polyarticular (20.44%) and 6 spondyloarthritis and systemic (13.64%). Sixteen (35.4%) had positive ANA titers, but only 4 (9.1%) had uveitis.

Remission during the Covid-19 pandemic

From January 2020 to July 2021, the in-person visits for patients with JIA were maintained in our center, although some appointments were conducted by phone due to the pandemic. When a flare was suspected during a phone appointment, a mandatory in-person visit was scheduled within a short time (no more than a week). Likewise, no patients had more than two consecutive phone visits, even if they did not have a flare. For this study, we included clinical data from in-person visits only.

A comparison between patients who flared vs. patients with stable remission over the 18-month period are shown in [Table 2](#). Patients who flared had a shorter remission duration and were receiving methotrexate as treatment.

Sixty-one patients (74%) met Wallace stable remission criteria prior to study period. A total of 57 patients (69.5%) fulfilled remission criteria at every visit during the 18 months of the study. Most of these patients had either no systemic treatment (27 cases; 43.6%) or biological therapy (23; 40.4%).

There were 25 patients (30.5%) who experienced a flare during the 18 months of the study. The mean age at disease onset of these patients was 3.95 years old and 18 (72%) were female. The most frequent treatments that they were receiving at the time of the flare were biological therapy (11 patients; 44%) and methotrexate (9 patients; 36%).

Moreover, out of the 44 patients who achieved stable remission for 3 years or more (as previously described), 10 (22.73%) had a flare during the 18 months of the study follow-up period. Regarding the treatment strategy on these 10 relapse patients, 4 had not received any systemic treatment yet. There were 8 patients on remission with methotrexate, and 3 (37.5%) of them had a flare, while 12 patients were on remission with biologics, and 3 (25%) of them flared up during the study.

There were no differences between patients regarding the JIA diagnosis when it came to remission survival rates ([Fig. 2](#)). The hazard ratio (HR), taking oligoarticular JIA as reference, was HR:0.89 (0.33–2.38) for the polyarticular course, HR:1.2 (0.38–3.76) for the spondyloarthritis group and HR:0.3 (0.04–2.2) for systemic JIA.

However, there were differences when considering the treatment at the beginning of the study, with patients who received methotrexate being more likely to experience a flare ($p:0.012$) compared to those treated with biologics or no treatment at all ($p:0.019$) ([Fig. 3](#)).

Using the subgroup without treatment as a reference, the HR of flaring when the patients were on methotrexate was 8.16 (2.52–26.3) and 3.63 (1.14–11.57) when receiving biologics.

Discussion

Stable remission is a realistic and achievable goal for JIA patients, although flares can still frequently persist. Our main objective was to evaluate remission survival in a cohort of JIA patients and to describe which factors might influence remission or relapse, in an attempt to bridge the gap between reality and current clinical

Table 1
Demographic characteristics of juvenile idiopathic arthritis (JIA) patients included in the study according to the treatment received.

| | Total (n:82) | No treatment(n:31) | Methotrexate(n:17) | Biologic therapy(n:34) | 'p' |
|-----------------------------------|--------------------|--------------------|---------------------|------------------------|------------------|
| Age at disease onset Median (IQR) | 4.49 (2.48–8.22) | 4.61 (2.55–6.91) | 7.42 (3.08–9.2) | 4.02 (2.35–8.93) | 0.36 |
| Age at study onset Median (IQR) | 12.09 (9.09–15.76) | 11.59 (9.06–13.93) | 12.91 (10.23–14.96) | 13.4 (8.79–16.41) | 0.90 |
| Sex (female) N (%) | 56 (68.29) | 18 (58.06) | 14 (82.35) | 24 (70.59) | 0.21 |
| Uveitis N (%) | 9 (10.98) | 6 (10.5) | 0 | 3 (12) | 0.16 |
| ANA N (%) | 31/79 (37) | 22 (40.7) | 7 (41.2) | 9 (36) | 0.33 |
| FR+ | 3/79 (3.66) | 1 (0.03) | 2 (11.76) | 2 (5.89) | 0.52 |
| ACCP+ | 3/71 (3.66) | 0 | 2 (11.76) | 3 (8.82) | 0.19 |
| Time in remission Median (IQR) | 3.53 (1.8–5.35) | 3.8 (2.01–6.21) | 2.8 (1.69–4.21) | 2.07 (1.69–4.52) | 0.003 |
| Flares during 18 months N (%) | 25 (30.49) | 5 (16.13) | 9 (52.94) | 11 (32.35) | 0.028 |
| Previous treatments N (%) | | | | | |
| Steroids | 5 (6.1) | 5 (16.13) | 0 | 0 | 0.13 |
| Joint injections | 37 (45.12) | 9 (29.03) | 12 (70.59) | 16 (47.06) | 0.12 |
| Methotrexate | 75 (91.46) | 24 (77.42) | 17 (100) | 34 (100) | 0.001 |
| Biologics | 50 (60.98) | 8 (25.81) | 8 (47.06) | 34 (100) | <0.001 |
| JIA groups N (%) | | | | | |
| Oligoarticular | 39 (45.12) | 16 (51.61) | 9 (52.94) | 14 (35.29) | 0.32 |
| Polyarticular | 25 (30.49) | 4 (12.91) | 5 (29.41) | 16 (47.06) | 0.01 |
| Spondyloarthritis | 7 (8.54) | 2 (6.46) | 2 (11.76) | 3 (8.82) | 0.19 |
| Systemic | 11 (13.41) | 8 (25.81) | 1 (5.88) | 2 (5.88) | 0.08 |

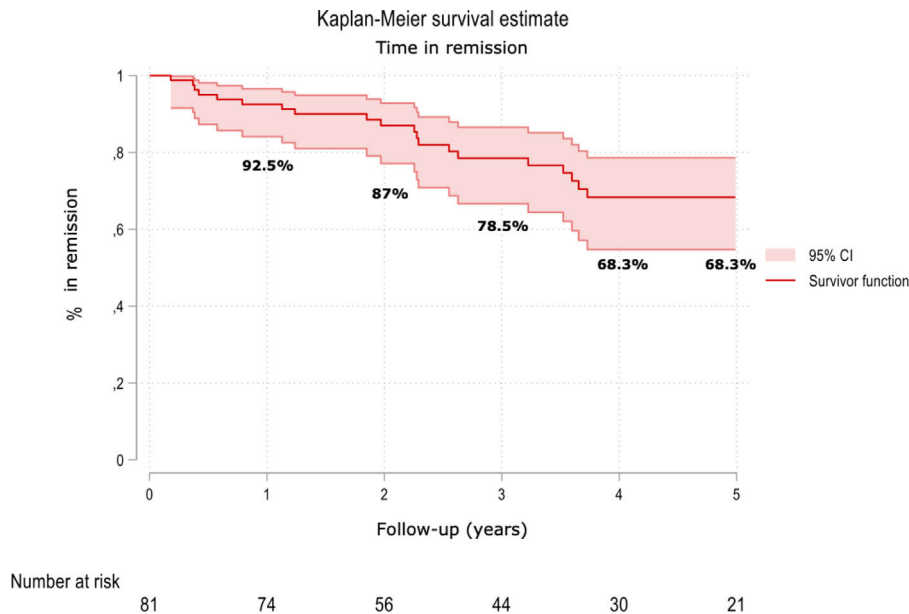


Fig. 1. Remission survival along years.

Table 2
Demographic characteristics of juvenile idiopathic arthritis (JIA) patients included in the study, divided depending on the occurrence of flares.

| | Total (n:82) | Remission (n:57) | Flared (n:25) | 'p' |
|-----------------------------------|--------------------|-------------------|------------------|--------------|
| Age at disease onset Median (IQR) | 4.49 (2.48–8.22) | 4.55 (2.47–7.42) | 3.95 (2.93–9.25) | 0.119 |
| Age at study onset Median (IQR) | 12.09 (9.09–15.76) | 12.84 (9.9–15.78) | 11 (8.42–14.96) | 0.441 |
| Sex (female) N (%) | 56 (68.29) | 38 (66.7) | 18 (72) | 0.632 |
| Uveitis N (%) | 9 (10.98) | 6 (10.5) | 3 (12) | 0.844 |
| ANA N (%) | 31 (37) | 22 (40.7) | 9 (36) | 0.688 |
| FR+ | 3/79 (3.66) | 2 (3.50) | 1 (4) | 0.755 |
| ACPA+ | 3/71 (3.66) | 1 (1.75) | 2 (8) | 0.826 |
| Time in remission Median (IQR) | 3.53 (1.8–5.34) | 3.8 (2.01–6.21) | 2.58 (1.62–3.94) | 0.017 |
| Treatment at study onset | | | | 0.015 |
| None N (%) | 32 (39.02) | 27 (43.6) | 5 (20) | 0.019 |
| Methotrexate N (%) | 16 (19.51) | 7 (12.3) | 9 (36) | 0.012 |
| Biologics N (%) | 34 (41.46) | 23 (40.4) | 11 (44) | 0.757 |
| ILAR JIA subcategory N (%) | | | | 0.359 |
| Oligoarticular | 37 (45.12) | 24 (43.6) | 13 (52) | 0.486 |
| Polyarticular | 25 (30.49) | 17 (30.9) | 8 (32) | 0.922 |
| Spondyloarthritis | 7 (8.54) | 4 (7.3) | 3 (12) | 0.487 |
| Systemic | 11 (13.41) | 10 (18.2) | 1 (4) | 0.087 |
| Isolated uveitis | 2 (2.44) | 2 (3.5) | 0 (0) | 0.315 |

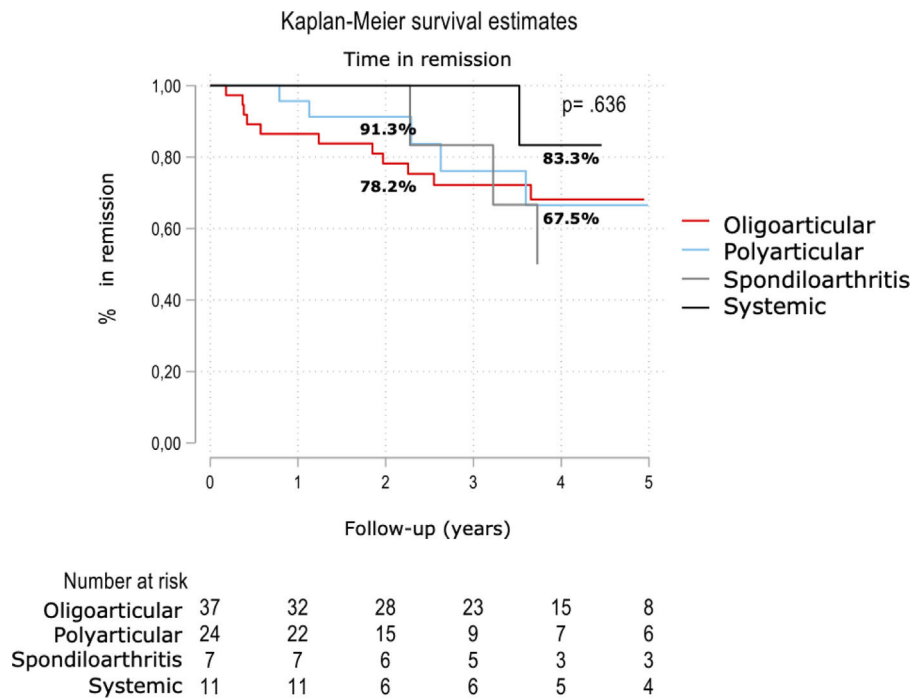


Fig. 2. Remission survival according to the ILAR subcategory.

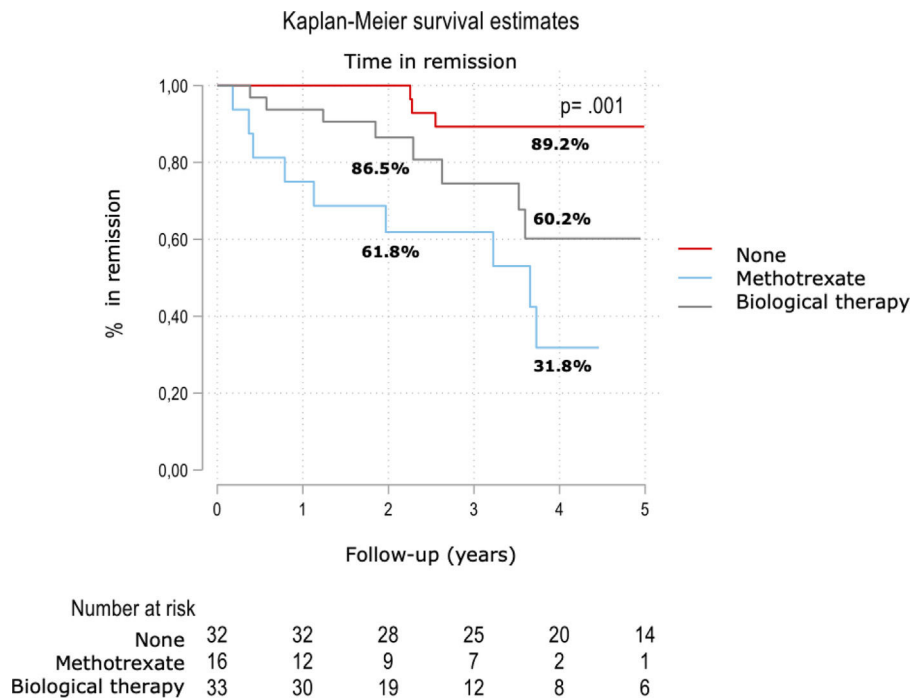


Fig. 3. Remission survival according to the treatment received at the beginning of the study.

knowledge when it comes to patient remission in clinical practice. Our study showed that 69.5% of the patients maintained stable clinical remission during the 18 months of follow-up. When remission survival was retrospectively analyzed a high proportion of the patients maintained remission after 5 years (68.3%). Stable remission was more likely to be sustained the longer the patient had been without disease activity at time of study onset (3.8 vs. 2.6 years of remission) regardless of disease duration, although the remission period was still longer in both groups. Although in the literature

the likelihood of remission is known to increase with illnesses of longer duration,¹⁶ we did not observe this in our cohort.

The demographic characteristics of our cohort were similar to other studies in similar populations.^{17,18} Female sex was predominant, the median age of disease onset was earlier than 6 years old (4.5 years old), and the most common JIA subtype was oligoarticular.

The type of treatment received seems to have some significance regarding the risk of flares. Patients who received methotrexate had a higher risk of flares than those who underwent biologic therapy

or went without treatment at all. Patients under biological therapy experienced an active and efficacious treatment, and were also more adherent, which explains the lower risk of flares. Patients who did not undergo any systemic treatment had a lower risk of flares than those treated with methotrexate, probably because the disease was less aggressive and because some of those patients had been treated early before, leaving their disease dormant. Unfortunately, we have no conclusive evidence regarding this aspect and can only guess at a possible correlation.

We found no significant differences between the JIA groups due to a lack of statistical power, although we did identify a trend ($p=0.08$) showing a lower remission duration in polyarticular JIA. In accordance with standard clinical practice, we found that those patients were also more likely to require biologic therapy, probable due to the fact that polyarticular JIA patients tend to have a more refractory disease course.¹⁹ Depending on the initial treatment given to them, an earlier and more stable remission can be achieved. Biologic therapies changed the clinical course in these patients and a combined therapy seems to be the best strategy to achieve earlier and more stable remission. Kimura et al.,²⁰ compared three treatment plans used for polyarticular JIA patients, and showed that if they are treated initially with combined therapy consisting of DMARDs and DMARDb, inactive disease is more likely to be achieved earlier. Alexeeva et al.,²¹ compare early combination therapy, specifically etanercept + methotrexate vs methotrexate + placebo, and also reported better remission rates with the former.

It has been observed that flares were less common in systemic JIA patients, with the remission survival rate being 5 years. Systemic JIA can range from a monocyclic course (the most common), with subsequent long-lasting complete remission, to persistently active disease into adulthood. However, the variabilities in clinical course, differences in its physiopathology and small sample sizes can make it difficult to compare systemic JIA with the rest of the subcategories.²² Our results contrast with other studies in which persistent oligoarticular JIA appeared to be the JIA subtype that most frequently achieved remission.^{17–24}

In a 434-patient cohort evaluated in a multicenter study during 18 years of follow-up, Glerup et al.,²⁵ also showed that persistent oligoarticular and systemic JIA had the highest proportions of clinical remission. Spondylarthritis was the JIA subtype with the lowest clinical remission rate (8.1%), as was the case in our cohort.

Remission survival was 92.5% at year one, 78.5% at 3 years and 68.3% at 5 years. We recorded high remission survival rates compared with other published studies.^{16,17,23,26} This can be explained by the fact that a high proportion of our patients were receiving systemic treatment (62.20%). It also reflects the results of early treatment strategy, which was less than four months when using methotrexate and a year and a half or less for biological therapies.

In a recently published paper, Castillo-Vilella et al.²⁶ evaluated 206 JIA patients in which the highest remission rate obtained was in those who received methotrexate. However, in our cohort, only 47% of patients with methotrexate achieved stable remission (18 months) compared to 67.6% and 84.4% patients with biologic DMARD and no treatment, respectively. Castillo-Vilella et al.²⁶ reported a higher biological naïve population (75%) than in our cohort (39%), which could explain some of the differences between the two studies. Moreover, their remission definition was based on the length of remission time per treatment, i.e., 6 months for JIA patients under systemic treatment and 12 months for patients without any systemic treatment. We defined remission as not having inflammation at any of the follow-up visits. This more flexible criteria may explain why 90% of our patients achieved stable remission compared to 70% of their patients.

Certain biomarkers can help predict flares, although they are not yet well defined. Some studies have suggested that the presence

of ANA antibodies can represent a favorable factor for achieving remission.^{27,28} However, this might be due to the fact that ANA-positive patients are usually younger at disease onset and frequently present a less aggressive clinical course. Other studies have concluded that ANA negativity is associated with a poor response to methotrexate.²⁹ On the other hand, other studies have been unable to demonstrate any differences in remission rates between ANA positive and negative patients.^{30,31} We have not found any differences in relation to either the presence of ANA titers or uveitis.

Certain limitations of our study should be kept in mind. The complexity of JIA and the small sample size of our study explain the low statistical power. Moreover, the mono-centric and non-controlled design might have led to treatment-selection bias. It is also important to note that we did not systematically assess treatment adherence via a questionnaire, and it is possible that some patients under systemic treatment discontinued it at some point during the study period. It would have been interesting to assess how the tapering or withdrawal of treatment influences flaring and remission. Unfortunately, we did not collect such data in the current study nor the exact doses of methotrexate, although the median range was 2.5–10 mg/week. However, the dynamic nature of treatment management in JIA makes it difficult to draw any conclusions regarding the impact of different treatments on remission. In addition, guidelines for the best way to taper and withdraw treatment in JIA patients are still needed.³² Finally, the short study time may also limit the results.

Conclusion

More than two-thirds (69.5%) of the patients were in stable remission during COVID-19 pandemic. The type of JIA has not influence on survival rates. However, it seems that patients under methotrexate treatment were more likely to experience a flare comparing to those under biologic therapies.

Authors' contributions

All authors contributed significantly to the design and redaction of the manuscript. All agreed on the final version.

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Conflict of interest

The authors declare no conflicts of interest related to this work.

Availability of data and materials

All data generated or analyzed during the study are included in this published article.

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