Spectrum of clinical research in Juvenile Idiopathic Arthritis: a cross-sectional analysis of registered studies in clinicaltrials.gov and clinicaltrialsregister.eu

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Abstract

Management of Juvenile idiopathic arthritis (JIA) has improved tremendously in recent years due to the introduction of new drug therapies but remains complex also in terms of non-pharmaceutical issues. In order to determine the direction of scientific progress by characterizing the current spectrum of ongoing clinical research in JIA, we analyzed all ongoing studies in the field of JIA registered in clinicaltrials.gov and clinicaltrialsregister.eu concerning sponsoring, enrollment, duration, localization, and particularly objectives. Close of database was 7 January 2021. After identifying doubled-registered studies, N=72 went into further analysis. Of these, 61.1% were academia-sponsored and 37.5% by pharma industry. The majority of studies was of interventional type (77.8%), while others (22.2%) were observational. Median planned enrollments were 100 participants (interventional studies) and 175 participants (observational studies), respectively. Duration differed remarkably from one month to more than 15 years with a median of 42.5 months. 61.1% of studies were located in a single country, 38.9% were in several. Europe and North America clearly dominated study localizations. Study objectives were DMARDs (56.9%), followed by diagnostics and disease activity measurement (18.1%), and medication other than DMARD (12.5%), besides others. Studies on DMARDs were mainly sponsored by industry, predominantly interventional studies on established and novel biologics, with several on specific issues like systemic JIA and others. The spectrum of registered studies is currently centered on drug therapy and diagnostics, while other issues in JIA play a subordinated role.

Keywords: juvenile idiopathic arthritis, research registry, clinical trial, DMARD
### Abbreviations:

| Abbreviation | Full Form |
|--------------|-----------|
| ABA          | abatacept |
| ADA          | adalimumab|
| ANA          | anakinra  |
| BAR          | baricitinib|
| CAN          | canakinumab|
| CER          | certolizumab|
| DMARD        | disease modifying anti-rheumatic drug |
| ETA          | etanercept |
| GOL          | golimumab |
| HCQ          | hydroxychloroquin |
| IFN          | interferon |
| IL           | interleukine |
| IXE          | ixekizumab |
| JAK          | janus kinase |
| JIA          | juvenile idiopathic arthritis |
| MTX          | methotrexate |
| n/a          | not available |
| RA           | rheumatoid arthritis |
| SAR          | sarilumab |
| SEC          | secukinumab |
| SUL          | sulfasalazine |
| TNF          | tumor necrosis factor |
| TOC          | tocilizumab |
| TOF          | tofacitinib |
| UPA          | upadacitinib |


Introduction

Juvenile idiopathic arthritis (JIA) is one of the most prevalent chronic diseases in childhood with 16-150 cases per 100,000 population in developed countries [1]. The commonly used classification by the International League of Associations for Rheumatology divides JIA into seven subgroups [2]. Besides many similarities in clinical presentation and pathophysiology among different subgroups, JIA may also be seen as a collective term for separated disease entities, namely when regarding systemic JIA, psoriatic arthritis, and enthesitis-related arthritis in contrast to oligo-/polyarthritis [1-3]. Sometimes even in absence of any joint involvement, JIA can be diagnosed or suspected (in case of a probable systemic JIA [4]). Especially JIA associated uveitis and temporomandibular joint involvement are prevalent challenging treatment issues [3,5].

Under-treated JIA results in joint corrosion, reduced quality of life and participation, and may cause persistent disabilities [3,6,7]. While many of these complications can also be found in adult patients with rheumatoid arthritis (RA), pediatric patients furthermore are at risk for local growth disturbances, (general) growth failure, and pubertal disorders [1,8]. JIA associated uveitis can result in irreversible visual loss, and the most frequent subgroup of JIA is the most vulnerable for developing uveitis [1,9].

From the young patients’ view, an early diagnose and prompt start of a sufficient treatment is essential not only to improve current complaints, but also to improve long-term outcome. I.e., early treatment with disease-modifying antirheumatic drugs (DMARDs) is associated with better disease control and drug-free remission in young adulthood [10]. Early response to treatment is associated with better long-term outcome [11,12].

The last decades tremendously improved management of JIA [13]. Molecular-immunology studies on disbalances between immune tolerance and inflammation, genetic susceptibility and gene expression lead to better understanding of etiologies and pathogeneses [14]. Introduction of biologic DMARDs revolutionized treatment and outcome of JIA patients and will likely be applied in personalized treatment strategies [3,15]. From the care providers’ view – the pediatric rheumatologist – scientific research and drug development are brought into practice through structural establishment of pediatric rheumatology networks and disease registers, and emerging guidelines for JIA [1,3,4,16-19].

Despite these considerable advancements, treatment of JIA remains complex and improvable, and still a relevant part of patients is refractory to treatment. Better definition of disease entities and their pathogeneses are needed for improved classification and treatment strategies [1,16], as well as specific biomarkers for personalized treatment tuning [3,16,20,21]. Pediatric-approved DMARDs require long-term observation through registry studies [22] and recently approved DMARDs from adult medicine – i.e. in the treatment of rheumatoid arthritis – need to be explored for their potentials and risks in pediatric patients with JIA [23]. Novel drugs targeting selectively molecules or pathways involved in
inflammation are needed to offer new treatment perspectives in refractory cases, therefore prospective clinical studies are inevitable [3,16].

But improving pediatric rheumatologic care is more than improving pediatric pharmacological care. Besides all available possibilities of modern treatment, a nontrivial question is how to provide individual access to pediatric rheumatologic care for children with such diseases [24,25]. And, as pediatricians are not treating small adults, improving pediatric-specific issues must be addressed like family-centered care, social integration and rehabilitation, as well as transition as a key issue of every chronic pediatric disease [26].

We therefore directed our efforts in determining the direction of progress in the field. Specifically, the purpose of this study is to characterize current clinical research in the field of JIA in regard to pediatric medical needs. We hypothesize that research hereon is drug-driven due to its achievements in recent years and potential economic prospects.
Materials and Methods

Aim of the study

This study aims to characterize ongoing clinical studies in the field of JIA in terms of sponsoring, enrollment, duration, localization and investigational topics, in a cross-sectional analysis. STROBE criteria (Strengthening the Reporting of Observational studies in Epidemiology) were applied for design, conduction and reporting of this study [27]. The term ‘ongoing’ refers to not yet finally completed studies at time of analysis.

Search for clinical studies

Web-based databases of the U.S. National Library of Medicine (clinicaltrials.gov) and the European Union Clinical Trials Register (clinicaltrialsregister.eu) were assessed for ongoing clinical studies with the search keywords ‘juvenile idiopathic arthritis’, synonyms ‘JIA’ and ‘juvenile chronic arthritis’. Filters were applied for age range (all age groups under 18 years) and study status (‘Recruiting’, ‘Not yet recruiting’, ‘Active / not recruiting’, ‘Enrolling by invitation’, ‘Suspended’, and ‘Ongoing’, ‘Restarted’, ‘Temporarily halted’, respectively).

Databases were closed for search 7 January 2021 and data were downloaded for further analysis.

Data analysis

Microsoft Excel 2019 MSO, Edmond, US-WA, was used for data analysis. Standard techniques for descriptive statistics were applied. Study titles and description details were analyzed concerning sponsor, enrollment, duration, localization of study centers, and study type and objectives. Double-registered studies were identified, doublets were excluded. Missing data were not imputed. Sponsor was categorized into either industry or academia (including universities, public institutions and hospitals). Planned enrollment of participants was also extracted from description details. By the start date ongoing ‘duration’ of studies was calculated in months using the earlier date in case of doublets in both registries. For localization of study centers we displayed the top five locations for single and multi-country studies, respectively, for which countries were clustered to their super-ordinated medical authorities (i.e., EU countries – EMA). Study details were analyzed for classification of interventional or observational studies, and their clinical phases where appropriate. For determination of study objectives keywords were generated from study descriptions, and content analysis was used to determine answer categories [28].
Results

Registered studies

Overall, n=56 studies registered on clinicaltrials.gov and n=34 studies on clinicaltrialsregister.eu met the search criteria. Of these, n=18 studies were identified being double-registered. Contents of n=72 studies were further analyzed. In the following passage we present the main results, for more details see Supplement 1.

General findings

Sponsor

Academia sponsored 44/72 (61.1%) of found studies, industry 27/72 (37.5%), one study was mixed sponsored. Of academia-sponsored studies, 3/44 (6.8%) were doubled-registered in both registers as well as 15/27 (55.6%) of industry-sponsored studies.

Planned Enrollment

For interventional studies, the planned enrollment was median 100, with a minimum of 6 and a maximum of 340 participants. Planned enrollment for observational studies was median 175, with a minimum of 10 and a maximum of 9,000 participants.

Duration of studies

Start dates of n=2 studies were given in the future at time of assessment and therefore not used for calculation of duration. Duration of ongoing studies was calculated from n=70 studies with a median of 42.5 months, a minimum of 1 month and a maximum of 183 months (more than 15 years).

Locations

Of analyzed studies, 44/72 (61.1%) were located in a single country and 28/72 (38.9%) in multiple countries. Most frequent countries for single location were: France (9/44), Netherlands (6/44), United States of America (6/44), Canada (5/44), China (3/44), and Italy (3/44). When multiple countries were involved, most frequent countries were: EU countries (24/28), United Kingdom (17/28), Russian Federation (14/28), Mexico (13/28), and the United States of America (13/28). Geographically, European countries were involved in
54/72 studies (75.0%), North American countries in 30/72 studies (41.7%), South American as well as Asian countries in 14/72 studies (19.4%) each, African countries in 8/72 studies (11.1%), and Australia and Oceania in 6/72 studies (8.3%).

**Study types**

The found study type was interventional in 56/72 (77.8%), and observational in 16/72 (22.2%) studies. A clinical phase was given in \(N=44/56\) of interventional studies:

- Phase I: 5 studies,
- Phase II: 4 studies,
- Phases I+II: 3 studies,
- Phase III: 22 studies,
- Phase IV: 10 studies.

**Study objectives**

For proportions of study objectives see also Figure 1.

**DMARDs**

41/72 (56.9%) studies were related to DMARDs in the fields of JIA including JIA associated uveitis; industry sponsors were involved in 27/41 studies; 14/41 studies were sponsored by academia only. Studies addressed conventional, non-biological (hydroxychloroquine, methotrexate, sulfasalazine; 10/41 studies) and/or biological DMARDs (37/41 studies). Vice versa, 31/41 studies did not involve any non-biological DMARD as a variable or control, and 4/41 studies did not involve any biological DMARD, see also Figure 2.

Only 5/41 studies were of observational type, all others were interventional. The following DMARDs were specifically studied in these studies, in descending order (partly multiple agents involved per study):

- Methotrexate (MTX; 10/41 studies, hereof three observational studies),
- Abatacept (ABA; 6/41 studies, hereof one observational study),
- Etanercept (ETA; 6/41 studies),
- Tocilizumab (TOC; 6/41 studies),
- Adalimumab (ADA; 6/41 studies, hereof one observational study),
- Baricitinib (BAR; 4/41 studies),
- Tofacitinib (TOF; 3/41 studies),
- Canakinumab (CAN; 2/41 studies),
- Golimumab (GOL; 2/41 studies, hereof one observational study),
- Sarilumab (SAR; 2/41 studies),
- Secukinumab (SEC; 2/41 studies),
- Anakinra (ANA; 1/41 study),
- Certolizumab (CER; 1/41 study),
- Hydroxychloroquine (HCQ; 1/41 study),
- Ixekizumab (IXE; 1/41 study),
- Sulfasalazine (SUL; 1/41 study),
- Upadacitinib (UPA; 1/41 study).

Of studied biological agents, corresponding biological targets are shown in Figure 3 (interventional and observational studies). Of all studies on DMARDs, 10/41 studies specifically addressed treatment of systemic JIA (DMARDs: ANA, BAR, CAN, MTX, SAR, TOC, and TOF), 4/41 studies specifically addressed enthesitis-related and psoriatic JIA (DMARDs: ETA, IXE, SEC), and 3/41 studies specifically addressed JIA associated uveitis (DMARDs: ADA, BAR, GOL). Withdrawal strategy was an explicit issue in 6/41 studies (DMARDs: ABA, ADA, ANA, ETA, MTX, TOC).

Enrollment of observational studies was median 833, with a minimum of 10 and a maximum of 9,000. For clinical phases and planned enrollments in interventional studies on biological DMARD agents see Table 1. All industry-sponsored studies were located in multiple countries; whereas only two of the academia-sponsored studies had locations in more than one country (USA + UK and several EU countries, respectively).

Diagnostics and measurement of disease activity

13/72 (18.1%) studies were related to diagnostics and disease activity in JIA in a broader sense. All these studies were academia-sponsored and located in a single country. Five of these studies concerned musculoskeletal and bone involvement (three interventional, two observational studies), two studies each concerned differential diagnose to septic arthritis (both observational), imaging of arthritis (both observational, MRI and ultrasound, respectively), and temporomandibular involvement (both observational), as well as one study each on etiology and pathogenesis of systemic JIA (observational), disease activity biomarker (interventional), and a national disease registry (observational). Enrollment of these studies was median 90, with a minimum of 30 and a maximum of 1,000.

Medication other than DMARD

9/72 studies (12.5%) were related to medications other than DMARD and all of them of interventional type, concerning the following medications: anti-IFN-gamma in systemic JIA (phase II), dexmedetomidine (phase IV; as sedative during joint-injections), mesenchymal stromal cells (phases I and II), genicular nerve block (phase IV), high-dose nicotinamide...
(phases I and II), ondansetron (phase n/a; as pre-medication), probiotics (phase n/a), recombinant interleukine 2 (phase n/a), triamcinolone hexacetonid (phase IV). Except for the study on anti-IFN-gamma, studies were academia-sponsored and located in a single country. Enrollment of studies was median 104, with a minimum of 6 and a maximum of 202.

Non-medication treatment

6/72 studies (8.3%) were related to non-medication treatment of JIA and of interventional type: three studies concerned sleep self-management of JIA patients, as well as one study each on yoga and aerobic dance for pain management, a dietary intervention with specific carbohydrates, and a peer mentoring program for adolescents with JIA. All these studies were academia-sponsored and located in a single country. Enrollment was median 30, with a minimum of 18 and a maximum of 262.

Vaccination

2/72 studies (2.8%) were related to JIA and vaccination: one observational study concerned frequency of human papilloma virus vaccination among JIA patients, and one interventional study concerned safety and efficacy of live attenuated measles, mumps, rubella vaccine in JIA patients. Both studies were academia-sponsored and located in France and Netherlands, respectively. Enrollment was 150 and 280, respectively.

COVID-19 pandemic

One observational, academia-sponsored study (1.4%) was related to the COVID-19 sanitary crisis and observed the impact on therapeutically management of JIA patients. Localized in France, its enrollment was 150.
Discussion

Current clinical research in JIA was mainly focused on drug therapy—which predominantly means DMARD agents and sponsoring by pharmaceutical industry—, followed by studies on diagnostics and measurement of disease activity. Non-medication therapy and other issues were clearly secondary. In general, the size of interventional clinical studies was relatively small with a maximum enrollment of 340 participants. The two main study locations were Europe and North America, followed by South America and Asia.

Role of sponsor in clinical studies

Ongoing registered clinical studies were sponsored by academia in about 60%, and by (pharma) industry in about 40%. Industry-sponsored studies were doubled-registered in both registries in slightly more than half of the cases, which is not common for academia-sponsored studies.

Industry-sponsored studies almost exclusively studied DMARDs, except for one study that concerned treatment with anti-IFN gamma in systemic JIA. Only two of the industry-sponsored studies were observational (pharmacovigilance on MTX, ABA, ADA) while most others interventional tested DMARDs namely BAR, CER, IXE, SAR, SEC, TOF, and UPA for introduction into treatment of JIA. Usually drugs had recently been labeled for rheumatic or chronic inflammatory bowel diseases in adults first, and now been exploratory used for JIA patients [23]. Only few interventional studies sponsored by the industry concerned longer established DMARDs in JIA, TOC above all. All industry-sponsored studies had localizations in more than one country; we assume that this might be due to greater access to potential participants as well as potential pharma markets.

Academia-sponsored studies did have much more various objectives. Most of the observational studies (14/16) were done by academia, especially in the fields of diagnostics and disease activity measurement. At least one-third of research in DMARDs is performed by academia, in fact on longer established drugs including non-biological DMARDs. Interestingly, withdrawal strategies in DMARD-treated patients play a significant role. Besides treatment with DMARDs, academia explores others possibilities of JIA treatment including non-DMARD medications and non-medication (behavioral) treatment strategies. Multi-lateral localizations were an exceptional condition here; we assume that barriers between heterogenous legal areas increase necessary effort for realization of multilateral collaboration beyond feasibility for academia in many cases.

Role of (novel) DMARDs in clinical studies
In clinical studies in the field of JIA – not surprising – DMARDs are the big player. Introduction of first conventional, non-biological agents, and later of biological DMARDs tremendously changed the game up to today [3,13,15]. Not only improvement of complaints and disabilities is longer goal of treatment, but complete disease control for best long-term outcome. Most frequent targets in DMARD treatment (in count of registered studies and enrollments) are TNF, JAK, IL-6, and T cell. Regarding novel DMARDs in JIA, especially Baricitinib and Tofacitinib seem to be the most promising agents regarding the size of enrollments in phase III studies. In contrast, IL-17 agents (IXE, SEC) did have distinctly fewer phase III studies and smaller enrollments. In addition, new agents were also tested for targets with longer available DMARDs, namely on TNF (Certolizumab, phase III) and IL-6 (Sarilumab, phase II). Furthermore, studies on IL-1 antagonist agents had a smaller part in DMARD studies.

Targeting specific issues in JIA

As mentioned in the introduction of this manuscript, JIA has unique challenges that differ from rheumatic diseases in adults [1,3,5,9]. Interference of JIA with the growing and developing body is under investigation in a few clinical studies on diagnostics of musculoskeletal impairment. Frequent prevalent issues in JIA like temporomandibular involvement and JIA associated uveitis were found being specific objectives in only a few clinical studies in this study. Most of the studies included several subgroups of JIA, mainly all non-systemic forms or poly-/ oligoarticular course of JIA. Nevertheless, systemic JIA was specifically addressed in 12/72 studies (ten concerning DMARDs). Likewise, etiological differing entities like psoriatic and enthesitis-related arthritis were specifically addressed in 4/72 studies (all on DMARDs).

Does clinical research meet the need for research in JIA?

It is not surprising that the majority (more than three quarters) of ongoing studies investigates particular treatment strategies on JIA. The value of scientific networking and collaboration, that brings research results into practice through guidelines and on-site rheumatologic care providers, can barely be shown by analyzing registered clinical studies. Family-centered care, social integration and rehabilitation, as well as transition were not found being explicit issues in ongoing studies. Especially transition in a vulnerable life stage is important for long-term outcome and of relevance in chronic-diseases in pediatrics in general [29], and of JIA in specific, including somatic and mental health [26,30,31]. A direct relation to adolescents in specific, for instance, was only found in one of the studies, although not in the context of transition but of peer-mentoring.
Limitations of this analysis

This study has several limitations. We used two registries (clinicaltrials.gov and clinicaltrialsregister.eu) by which studies registered in smaller national registries will be missing, as well as from central registries outside Europe and North America. Our study can naturally not determine studies and research that is not registered in any registry of clinical studies, which may be the case especially for non-medication and/or observational studies. Our analyzes rely on the accuracy of data input to these two registries. For the purpose of characterizing ongoing studies we did not consider studies that were finally closed for further recruitment. Neither we searched for specific terms, i.e. uveitis, what may had revealed more research in these specific fields. We consider this study a cross-sectional snapshot on the ongoing research in JIA in general, not a specific in-depth exploration on research in predefined subsets.
Conclusions

While clinical research is mainly focused on drug therapy and diagnostics, other issues in JIA management are marginal topics in registered studies.
### Tables and figures

Table 1: Registered interventional studies involving biologic DMARD agents, clinical phases and planned enrollments. *,† refer to studies involving multiple biological targets.

**IL interleukine, JAK janus kinase, TNF tumor necrosis factor**

| Target | DMARD | Phase | Registration number | Enrollment |
|--------|--------|-------|---------------------|------------|
| **TNF** | ADA / ETA | I     | NCT04585711         | 30         |
|        |        |       | NCT01421069         | 109        |
|        |        |       | NCT02840175*        | 62         |
|        |        |       | NCT03728478         | 260        |
|        |        |       | NCT03816397         | 118        |
|        |        | III   | EudraCT2009-012520-84 | 100    |
|        |        | IV    | EudraCT2013-003956-18† | 325     |
|        | CER    | III   | NCT01550003         | 193        |
|        | GOL    | III   | NCT02277444         | 130        |
| **JAK** | BAR    | III   | NCT03773965         | 190        |
|        |        |       | NCT03773978         | 197        |
|        |        |       | NCT04088396         | 103        |
|        |        |       | NCT04088409         | 40         |
|        | TOF    | I     | EudraCT2011-004914-40 | 24      |
|        |        | III   | NCT01500551         | 340        |
|        |        |       | NCT03000439         | 100        |
|        | UPA    | I     | NCT03725007         | 54         |
| **IL-6** | SAR    | II    | NCT02776735         | 100        |
|        |        |       | NCT02991469         | 72         |
|        | TOC    | III   | NCT02165345         | 82         |
|        |        |       | NCT02840175*        | 62         |
|        |        |       | EudraCT2007-000872-18 | 108      |
|        |        |       | EudraCT2009-011593-15 | 185     |
|        |        | IV    | NCT03301883         | 74         |
|        |        |       | EudraCT2012-000444-10 | 43      |
| **T cell** | ABA    | I/II  | NCT03733067         | 40         |
|        |        |       | NCT01844518         | 306        |
|        |        |       | NCT02840175*        | 62         |
|        |        |       | NCT03841357         | 187        |
|        |        | IV    | EudraCT2013-003956-18† | 325     |
| **IL-17** | IXE    | III   | NCT04527380         | 100        |
|        | SEC    | III   | NCT03769168         | 58         |
|        |        |       | EudraCT2016-003761-26 | 80     |
| **IL-1** | ANA    | IV    | EudraCT2015-004393-16 | 55      |
|        | CAN    | III   | EudraCT2008-005476-27 | 122     |
|        |        | IV    | EudraCT2018-004284-30 | 20      |
Figure 1: Proportions of registered study objectives.

Figure 2: Proportions of DMARD agents involved in registered studies.
Figure 3: Number of studies concerning biological DMARDs sorted for biological targets (interventional and observational studies, partly multiple agents involved per study). IL interleukine, JAK janus kinase, TNF tumor necrosis factor.
Funding Information
Not applicable.

Author Contributions
RL conducted the data analysis and interpretation, and wrote the draft of this manuscript. MR conceived of the study design, supervised data interpretation and revised the manuscript. Both authors approved the final manuscript.

Conflict of Interest
The authors declare to have no conflict of interest.

Ethics Statements
Not applicable.

Data availability statement
Underlying data of this study is fully available as supplement.
References

1. Ravelli, A.; Martini, A. Juvenile idiopathic arthritis. *Lancet (London, England)* 2007, 369, 767-778, doi:10.1016/s0140-6736(07)60363-8.

2. Petty, R.E.; Southwood, T.R.; Manners, P.; Baum, J.; Glass, D.N.; Goldenberg, J.; He, X.; Maldonado-Cocco, J.; Orozco-Alcala, J.; Prieur, A.M.; et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *The Journal of rheumatology* 2004, 31, 390-392.

3. Bridges, J.M.; Mellins, E.D.; Cron, R.Q. Recent progress in the treatment of non-systemic juvenile idiopathic arthritis. *Facility reviews* 2021, 10, 23, doi:10.12703/f/10-23.

4. Hinze, C.H.; Holzinger, D.; Lainka, E.; Haas, J.P.; Speth, F.; Kallinich, T.; Rieber, N.; Hufnagel, M.; Jansson, A.F.; Hedrich, C.; et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. *Pediatric rheumatology online journal* 2018, 16, 7, doi:10.1186/s12969-018-0224-2.

5. Covert, L.; Mater, H.V.; Hechler, B.L. Comprehensive Management of Rheumatic Diseases Affecting the Temporomandibular Joint. *Diagnostics (Basel, Switzerland)* 2021, 11, doi:10.3390/diagnostics11030409.

6. Guzman, J.; Oen, K.; Tucker, L.B.; Huber, A.M.; Shiff, N.; Boire, G.; Scuccimarrri, R.; Berard, R.; Tse, S.M.; Morishita, K.; et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. *Annals of the rheumatic diseases* 2015, 74, 1854-1860, doi:10.1136/annrheumdis-2014-205372.

7. Guzman, J.; Henrey, A.; Loughlin, T.; Berard, R.A.; Shiff, N.J.; Jurencak, R.; Benseler, S.M.; Tucker, L.B. Predicting Which Children with Juvenile Idiopathic Arthritis Will Have a Severe Disease Course: Results from the ReACCh-Out Cohort. *The Journal of rheumatology* 2017, 44, 230-240, doi:10.3899/jrheum.160197.

8. d'Angelo, D.M.; Di Donato, G.; Breda, L.; Chiarelli, F. Growth and puberty in children with juvenile idiopathic arthritis. *Pediatric rheumatology online journal* 2021, 19, 28, doi:10.1186/s12969-021-00521-5.

9. Saurenmann, R.K.; Levin, A.V.; Feldman, B.M.; Rose, J.B.; Laxer, R.M.; Schneider, R.; Silverman, E.D. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. *Arthritis and rheumatism* 2007, 56, 647-657, doi:10.1002/art.22381.

10. Minden, K.; Horneff, G.; Niewerth, M.; Seipel, E.; Aringer, M.; Aries, P.; Foeldvari, I.; Haas, J.P.; Klein, A.; Tatsis, S.; et al. Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood. *Arthritis care & research* 2019, 71, 471-481, doi:10.1002acr.23709.

11. Bartoli, M.; Tarò, M.; Magni-Manzoni, S.; Pistorio, A.; Traverso, F.; Viola, S.; Magnani, A.; Gasparini, C.; Martini, A.; Ravelli, A. The magnitude of early response to methotrexate therapy predicts long-term outcome of patients with juvenile idiopathic arthritis. *Annals of the rheumatic diseases* 2008, 67, 370-374, doi:10.1136/ard.2007.073445.

12. Oen, K.; Duffy, C.M.; Tse, S.M.; Ramsey, S.; Ellsworth, J.; Chédeville, G.; Chetaille, A.L.; Saint-Cyr, C.; Cabral, D.A.; Spiegel, L.R.; et al. Early outcomes and improvement of patients with juvenile idiopathic arthritis enrolled in a Canadian multicenter inception cohort. *Arthritis care & research* 2010, 62, 527-536, doi:10.1002acr.20044.

13. Hashkes, P.J. 50 Years Ago in The Journal of Pediatrics: Revolutionery Changes in the Management of Juvenile Idiopathic Arthritis. *The Journal of pediatrics* 2020, 224, 65, doi:10.1016/j.jpeds.2020.02.044.

14. Prakken, B.; Albani, S.; Martini, A. Juvenile idiopathic arthritis. *Lancet (London, England)* 2011, 377, 2138-2149, doi:10.1016/s0140-6736(11)60244-4.

15. Saougou, I.G.; Markatseli, T.E.; Voulgari, P.V.; Drosos, A.A. Current therapeutic options for the treatment of juvenile idiopathic arthritis. *Current rheumatology reviews* 2020, doi:10.2174/1573403x16999200917151805.
16. Rupert, N.; Martini, A. Current and future perspectives in the management of juvenile idiopathic arthritis. *The Lancet. Child & adolescent health* 2018, 2, 360-370, doi:10.1016/s2352-4642(18)30034-8.

17. Klein, A.; Minden, K.; Hospach, A.; Foeldvari, I.; Weller-Heinemann, F.; Trauzeddel, R.; Huppertz, H.I.; Horneff, G. Treat-to-target study for improved outcome in polyarticular juvenile idiopathic arthritis. *Annals of the rheumatic diseases* 2020, 79, 969-974, doi:10.1136/annrheumdis-2019-216843.

18. Ringold, S.; Angeles-Han, S.T.; Beukelman, T.; Lovell, D.; Cuello, C.A.; Becker, M.L.; Colbert, R.A.; Feldman, B.M.; Ferguson, P.J.; Gewanter, H.; et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis. *Arthritis & rheumatology (Hoboken, N.J.)* 2019, 71, 846-863, doi:10.1002/art.40884.

19. Horneff, G.; Klein, A.; Ganser, G.; Sailer-Höck, M.; Günther, A.; Foeldvari, I.; Weller-Heinemann, F. Protocols on classification, monitoring and therapy in children’s rheumatology (PRO-KIND): results of the working group Polyarticular juvenile idiopathic arthritis. *Pediatric rheumatology online journal* 2017, 15, 78, doi:10.1186/s12969-017-0206-9.

20. Choida, V.; Hall-Craggs, M.; Jebson, B.R.; Fisher, C.; Leandro, M.; Wedderburn, L.R.; Curtin, C. Biomarkers of Response to Biologic Therapy in Juvenile Idiopathic Arthritis. *Frontiers in pharmacology* 2020, 11, 635823, doi:10.3389/fphar.2020.635823.

21. Orczyk, K.; Smolewska, E. The Potential Importance of MicroRNAs as Novel Indicators How to Manage Patients with Juvenile Idiopathic Arthritis More Effectively. *Journal of immunology research* 2021, 2021, 9473508, doi:10.1155/2021/9473508.

22. Diener, C.; Horneff, G. Comparison of adverse events of biologics for treatment of juvenile idiopathic arthritis: a systematic review. *Expert opinion on drug safety* 2019, 18, 719-732, doi:10.1080/14740338.2019.1632288.

23. Singh, R.; Ivaturi, V.D.; Penzenstadler, J.; Liu, T.; Chen, J.; Marathe, A.; Ji, P.; Glaser, R.; Nikolov, N.; Sahajwalla, C. Response similarity assessment between polyarticular juvenile idiopathic arthritis and adult rheumatoid arthritis for biologics. *Clinical pharmacology and therapeutics* 2021, doi:10.1002/cpt.2218.

24. Chausset, A.; Pereira, B.; Echaubard, S.; Merlin, E.; Freychet, C. Access to paediatric rheumatology care in juvenile idiopathic arthritis: what do we know? A systematic review. *Rheumatology (Oxford, England)* 2020, 59, 3633-3644, doi:10.1093/rheumatology/kea438.

25. Consolaro, A.; Giancane, G.; Alongi, A.; van Dijkhuizen, E.H.P.; Aggarwal, A.; Al-Mayouf, S.M.; Bovis, F.; De Inocencio, J.; Demirkaya, E.; Flato, B.; et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *The Lancet. Child & adolescent health* 2019, 3, 255-263, doi:10.1016/s2352-4642(19)30027-6.

26. McColl, J.; Semalulu, T.; Beattie, K.A.; Alam, A.; Thomas, S.; Herrington, J.; Gorter, J.W.; Cellucci, T.; Garner, S.; Heale, L.; et al. Transition Readiness in Adolescents With Juvenile Idiopathic Arthritis and Childhood-Onset Systemic Lupus Erythematosus. *ACR open rheumatology* 2021, doi:10.1002/acr2.11237.

27. Vandenbroucke, J.P.; von Elm, E.; Altman, D.G.; Gøtzsche, P.C.; Mulrow, C.D.; Pocock, S.J.; Poole, C.; Schleselman, J.J.; Egger, M. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *International journal of surgery (London, England)* 2014, 12, 1500-1524, doi:10.1016/j.ijsu.2014.07.014.

28. Krippendorff, K. *Content analysis: an introduction to its methodology*, 2nd ed.; Sage: Thousand Oaks, CA, 2004.

29. Lestishock, L.; Nova, S.; Disabato, J. Improving Adolescent and Young Adult Engagement in the Process of Transitioning to Adult Care. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2021, doi:10.1016/j.jadohealth.2021.01.026.
Palman, J.; McDonagh, J.E. Young Minds: Mental Health and Transitional Care in Adolescent and Young Adult Rheumatology. *Open access rheumatology: research and reviews* **2020**, *12*, 309-321, doi:10.2147/oarrr.S228083.

McDonagh, J.E.; Farre, A. Transitional Care in Rheumatology: a Review of the Literature from the Past 5 Years. *Current rheumatology reports* **2019**, *21*, 57, doi:10.1007/s11926-019-0855-4.