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ORIGINAL ARTICLES

Biotechnological therapeutic in juvenile diopathic arthritis: pathophysiological implications and targeted therapies

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ABSTRACT

Objective: In this retrospective cohort study, we aim to investigate the most used biological disease modifying anti-rheumatic drugs (bDMARDs) in Juvenile Idiopathic Arthritis (JIA) patients in a pediatric rheumatologic unit from a Portuguese tertiary hospital, along with their effectiveness and safety. We also intended to link their effectiveness and the pathophysiology of the disease.

Methods: The medical records of JIA patients exposed to bDMARDs, between January 2018 and January 2023, in a pediatric rheumatologic unit from a Portuguese tertiary hospital were reviewed. Therapy effectiveness was accessed based on achievement of inactive disease according to Wallace Criteria. Effectiveness of different bDMARDs in the several JIA subtypes was linked to the disease´s pathophysiology. Adverse effects were also reviewed.

Results: Thirty-four patients were included in the study. Overall, nineteen patients (67,9%) had inactive disease at last evaluation. Six patients with missing data on inactive disease status were excluded from this analysis. Number of affected joints, ESR and CRP were significantly lower at 3, 6, 12 and 24 months after bDMARD therapy. All systemic JIA patients (n=10) were initially treated with Anakinra. Six (60%) achieved inactive disease. Two (20%) switched to Tocilizumab due to ineffectiveness in the control of articular features. Patients who switched to tocilizumab achieved inactive disease until the end of the follow-up. All patients with the other subtypes of JIA (n=24) were treated with TNF inhibitors. Inactive disease was achieved in 55,6%. Adverse effects occurred in eight patients (23,5%).

Conclusions: The results of the present study demonstrate the effectiveness of bDMARs in the study population. bDMARDs reduced the number of affected joints, CRP and ESR after three months of treatment, and this effectiveness was sustained over the two years of follow-up. For systemic JIA, preferred drug was Anakinra, an interleukin 1 inhibitor, and its effectiveness was consistent with previous studies. In the other JIA subtypes, TNF inhibitors were the most used bDMARDs, and showed an effectiveness consistent with previous studies. The most used bDMARDs for each JIA subtype are in line with pathophysiological differences. Our results demonstrated the safety of these drugs.

Keywords: Juvenile idiopathic arthritis, DMARDs, Adolescent rheumatology, Paediatric/Juvenile rheumatology, Biotechnological therapies

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease in pediatric age, affecting one in every 1000,000 children[1].

It is not a single disease, but a heterogeneous group of arthritis, of unknown etiology, that manifests itself before the age of 16 and persists for at least 6 weeks[1,2]. This heterogeneous group is currently classified into 7 subtypes of arthritis, with distinct pathophysiological characteristics. According to International League of Associations for Rheumatology criteria: systemic arthritis, oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, enthesitis-related arthritis, psoriatic arthritis and undifferentiated arthritis[1,3]. This subdivision allows for a better understanding of its pathogenesis and response to therapy[1,4].

The evident heterogeneity between the various subtypes of JIA, regarding their clinical features, genetic and pathophysiological characteristics, leads to different responses to currently available therapies[5,6]. The main differences arise between systemic arthritis and the other subtypes, as the pathophysiology of the latter is more consistent with an autoimmune disease[7].

In general terms, JIA therapy includes drugs, physiotherapy, occupational therapy, and psychosocial sup-

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port. Pharmacological therapy is based on nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids and conventional or biological disease modifying antirheumatic drugs (DMARDs)[8].

JIA therapy and its complications have undergone significant changes in the last decade, largely because of the introduction of these biotechnological DMARDs (such as tumor necrosis factor (TNF) inhibitors, interleukin 1 (IL-1) inhibitors, interleukin 6 (IL-6) inhibitors), resulting in a notable improvement in clinical *outcomes*[9].

Anti-TNFα therapy improves treatment outcomes for all forms of JIA, but it's notably less effective for systemic JIA, where the therapeutic approach has been IL-1/IL-6 signaling blockade[7]. Systemic JIA is associated with increased circulating levels of multiple cytokines[10,11], in which IL-1 plays a major role in the pathophysiology. Serum samples from these patients induce IL-1β transcription on healthy peripheral blood mononuclear cells (PBMCs), and treatment with the IL-1 receptor antagonists leads to the normalization of a disease-specific gene expression profile[12]. IL-1β is the cytokine from the IL-1 family with the most important role as a therapeutic target in several autoinflammatory diseases, such as systemic JIA. Blockage of IL-1β causes a quick and sustained decrease in inflammation. Other IL-1 family cytokines involved in the pathogenesis of systemic JIA are IL-1α, IL-6, IL-18, and IL-1 receptor antagonist (IL-1Ra). The main inflammatory cytokines involved in the pathophysiology of the other subtypes are distinct, with TNFα, IL17, IFNγ and IL23 having the major role in their pathophysiology[7].

As rare complication, some systemic JIA patients develop macrophage activation syndrome (MAS) during the course of the disease. This is a potentially lethal complication of chronic rheumatic diseases of childhood, in particular systemic JIA, that results from uncontrolled activation and proliferation of T lymphocytes and macrophages[13].

In the present study, we aim to analyze the most used biological DMARDs (bDMARDs) in JIA patients, in a pediatric rheumatologic unit from a Portuguese tertiary hospital, along with their effectiveness and safety. We also intended to link its effectiveness and the pathophysiology of the disease.

MATERIAL AND METHODS

In this retrospective cohort study, the medical records of patients with JIA in a pediatric rheumatologic unit from a Portuguese tertiary hospital were reviewed and those who were exposed to bDMARDs between January 2018 and January 2023, and that started this therapy before the age of 18 were selected. All data were collected between October 2022 and February 2023.

The date of the first bDMARD administration was considered the cohort entry. Patients were followed up for 2 years or until the end of the study.

Patients´ medical records were reviewed for age, sex, age at diagnosis, JIA subtype according to the European Alliance of Associations for Rheumatology criteria[2], presence of antinuclear antibodies (ANA), disease complications such as MAS, bDMARD therapy they were exposed to and other previous or concomitant drugs. To assess therapy effectiveness, the number of affected joints before bDMARD and at 3, 6,12 and 24 months after starting treatment, presence of uveitis, rash, fever, splenomegaly, serositis and generalized lymphadenopathy were reviewed. Biochemical parameters - CRP and ESR before therapy and at 3, 6,12 and 24 months were also collected. Inactive disease status was evaluated according to Wallace remission criteria for clinical remission in JIA[14].

The effectiveness of different bDMARD therapies in the several JIA subtypes was analyzed and linked with the disease´s pathophysiology. Adverse effects were also reviewed.

To reduce possible selection biases, a well-defined study population was established and patients were selected according to clear inclusion criteria. To address possible information biases, data on all variables were objective and collected from medical records.

Statistical analysis was performed using SPSS Statistics 27. Standard techniques for descriptive statistics were applied: median and interquartile range for continuous variables and frequencies and percentages for all discrete variables. Comparison of number of affected joints, CRP and ESR values before and at 3, 6, 12 and 24 months after starting bDMARD therapy was evaluated using Wilcoxon test. Remission status in systemic JIA patients and in the other subtypes of JIA was compared using Fisher´s exact test. Missing data were excluded from the analysis. Statistical significance was defined at the $p<0,05$ level.

This study was approved by the local ethics committee.

RESULTS

We reviewed medical records of 105 patients diagnosed with JIA, and a total of 34 patients were considered and confirmed eligible for this study. No patients were lost to follow up. Median age was 16 years old (interquartile range = 6,5) and median age at diagnosis was 8 years old (interquartile range = 9,5). 52,9% were girls. Mean follow-up time was 15,5 months. 9 (26,4%) patients

TABLE I. JIA subtypes in the study population (n=34)

	JIA subtype – n (%)
Systemic JIA	10 (29,4)
Enthesis-related arthritis	7 (20,6)
Psoriatic arthritis	6 (17,6)
Oligoarthritis	6 (17,6)
RF-negative polyarthritis	4 (11,8)
RF-positive polyarthritis	1 (2,9)

JIA – Juvenile Idiopathic Arthritis; RF – Rheumatoid factor

TABLE II. Number of affected joints, CRP and ESR values before and at 3, 6, 12 and 24 months after starting bDMARD therapy

Affected Joints	Median (IQR)	Missing data
Before therapy	3,0 (4,5)	6
3 months	0,0 (2,0)	11
6 months	0,0 (0,3)	8
12 months	0,0 (0,0)	15
24 months	0,0 (0,0)	19
CRP	**Median (IQR)**	**Missing data**
Before therapy	12,2 (44,3)	5
3 months	1,1 (2,4)	13
6 months	0,9 (1,2)	13
12 months	0,5 (1,4)	16
24 months	0,7 (1,5)	21
ESR	**Median (IQR)**	**Missing data**
Before therapy	30,0 (37,5)	5
3 months	10,0 (15,3)	16
6 months	10,0 (9,0)	13
12 months	10,0 (8,0)	17
24 months	9,5 (11,8)	20

IQR – Interquartile range; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate

had a documented history of active uveitis during the disease course and a total of 14 (41,2%) patients were ANA-positive.

Regarding the subtype of JIA, 29,4% had systemic JIA, 20,6% enthesis-related arthritis, 17,6% psoriatic arthritis, 17,6% oligoarthritis, 11,8% rheumatoid factor-negative polyarthritis and 2,9% rheumatoid factor-positive polyarthritis (Table I).

Of the total 34 patients, 21 (62%) previously or concomitantly received classic non-biologic DMARDs (Methotrexate and/or Sulfasalazine) and 23 (65%) patients previously received systemic corticosteroids.

The median time from diagnosis to the start of bDMARD was 12 months, with a minimum of 1 month, and a maximum of 7 years.

Overall, 61,2% of patients had inactive disease response at last evaluation.

The decrease in the number of affected joints was statistically significant (95% confidence interval) at 3 (p<0,001), 6 (p<0,001), 12 (p<0,001) and 24 (p<0,001) months after bDMARD therapy. ESR decrease was statistically significant after 3 (p<0,001), 6 (p=0,002), 12 (p<0,001) and 24 months (p<0,001) and CRP decrease was also statistically significant after 3 (p=0,006), 6 (p<0,001), 12 (p<0,001) and 24 (p<0,001) months of bDMARD therapy. Number of affected joints, CRP and ESR before and at 3, 6, 12 and 24 months after starting bDMARD therapy, as well as missing data for each variable is present in Table II.

For the remaining analysis, we set apart systemic JIA from the other categories, given the similar pathophysiology of the latter, and the distinct features of systemic JIA, which are more consistent with an autoinflammatory disease.

All (n=10) systemic JIA patients were initially treated with Anakinra, an IL-1 inhibitor, three of them due to MAS, three due inadequate response to glucocorticoids and four as initial therapy. Six (60%) of those had inactive disease at 3 months, two (20%) switched to Canakinumab, another IL-1 inhibitor, due to adverse effects, and two (20%) switched to Tocilizumab, an IL-6 inhibitor, due to ineffectiveness in the control of articular features after three months of therapy. These two patients simultaneously received methotrexate and achieved inactive disease status until the end of the follow up. At 24-months follow-up, all systemic JIA patients fulfilled inactive disease criteria. We had no missing data in inactive disease status of patients with systemic JIA.

Regarding patients with the other subtypes of JIA, all (n=24) were initially treated with TNF inhibitors: 67% with Adalimumab, 29% with Etanercept and 4% with Golimumab. One patient suspended Etanercept due to adverse effects, and switched to Rituximab, which was stopped due to ineffectiveness and adverse effects, and then switched to Tocilizumab. Ten (55,6%) patients had inactive disease at the end of follow-up. Of those who didn´t meet inactive disease criteria, 10% were non-compliant and 30% had started bDMARD shortly before the end of the follow-up. Data about inactive disease status was missing in 6 patients. Nineteen (79%) patients concomitantly received methotrexate until the end of the follow-up. The patients who did not receive concomitant methotrexate therapy had either enthesis-related arthritis subtype (four patients) or psoriatic arthritis subtype (one patient).

At the end of the follow-up, the percentage of patients who reached inactive disease was not significant-

ly different between patients with systemic JIA and the other subtypes (p=0.098).

Withdrawal of bDMARDs was attempted in five patients. In two systemic JIA patients receiving Anakinra, this drug was tapered and discontinued after two years of inactive disease under treatment. These patients had to restart bDMARD therapy due to systemic JIA flare, in one case one month after withdrawal and the other after two months. In one other systemic JIA patient, withdrawal was attempted after three years of inactive disease, and, in this case, disease status remained inactive until the end of follow-up. In one oligoarticular JIA patient receiving Etanercept, this drug was suspended after two years of inactive disease but was reintroduced after one month due to recurrence of arthritis. Lastly, in one psoriatic JIA patient, Adalimumab was discontinued after two years of inactive disease and the patient maintained inactive disease status until the end of follow-up. Among the patients in which bDMARD was reintroduced, one had history of active uveitis, whereas in the group of patients who maintained inactive disease status none had history of uveitis. All patients who flared after withdrawal were ANA positive, whereas among the two patients who did not flare, one was ANA-positive and the other was not. The average time since diagnosis until biological treatment was 4 years in relapsed patients and 2,5 years in non-relapsed patients.

Adverse effects were observed in eight patients (23,5%). In six of these cases, adverse effects were considered mild and did not lead to a change in medication: four patients reported pain during the administration, one patient reported nausea with Adalimumab and one patient had mild neutropenia secondary to Anakinra. More serious adverse effects occurred in 2 patients: two patients presented a toxic hepatitis secondary to Anakinra; one patient developed a lupus-like membranoproliferative glomerulonephritis while receiving Etanercept and later a persistent hypogammaglobulinemia secondary to Rituximab, requiring replacement therapy with human immunoglobulin, primary immunodeficiencies were excluded.

DISCUSSION AND CONCLUSIONS

The results of the present study demonstrate the effectiveness of bDMARDs in the study population. These drugs reduced the number of affected joints, CRP and ESR after three months of treatment, and this effectiveness was sustained over the two years of follow-up. Most patients met the remission criteria after the introduction of bDMARDs and some of those who did not meet them was either because they were receiving bDMARDs for a short time or because they did not comply with therapy.

In systemic JIA, the preferred drug was Anakinra, an IL-1 inhibitor. Current evidence supports early use of monoclonal antibodies or soluble receptors to block inflammatory cytokines in patients with systemic JIA. Of these, the most efficacious biologic agents, based upon results from randomized trials, are those that block interleukin IL-1 or IL-6 [15]. The 2021 American College of Rheumatology (ACR) guidelines for treatment of systemic JIA conditionally recommend IL-1 or IL-6 inhibitors as initial monotherapy and strongly recommend them over a single or combination of classic synthetic DMARDs for systemic JIA patients without MAS with inadequate response to or intolerance of NSAIDs and/or glucocorticoids. However, in the absence of sufficient controlled studies, no preferred agent has been endorsed[16]. For systemic JIA with MAS, IL-1 or IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS, but again no preferred agent has been indicated[16]. In our study sample, Anakinra was first option in all systemic JIA patients, either as initial therapy, as subsequent therapy in patients with poor disease control or as MAS adjuvant therapy. This may be explained by its short half-life, that enables a prompter dose adjustment or therapy withdrawal, if the patient does not respond[17] and by its lower cost in Portugal, when compared to other IL-1 or IL-6 inhibitors. Also, Anakinra is safe to administer in patients with suspected systemic JIA in which some differential diagnosis (including infectious, malignant or hereditary autoinflammatory diseases) haven´t been fully excluded yet[18]. Nevertheless, Anakinra requires daily subcutaneous injections with frequent local adverse reactions, and some patients prefer other therapeutic options that require less frequent administrations[16]. Previous studies report an efficacy of Anakinra ranging between 55 and 70%, which is consistent with the results of our study[19,20].

Evidence shows these biologics are effective for most children with this disease, but further research is needed regarding which should be used, given different patient characteristics[17]. In patients who have incomplete response or intolerance to the first bDMARD, 2021 ACR guidelines for the treatment of JIA recommend switching to an alternative IL-1 or IL-6 inhibitor, but there is no preferred agent, and it is not indicated whether it is better to switch to another bDMARD of the same class or to a different class[18]. In this study population, the two patients receiving Anakinra who failed in controlling articular features switched to another class – IL-6 inhibitor Tocilizumab – and achieved inactive disease. In fact, IL-6 induces inflammatory cell differentiation

and activation, osteoclast activation and periarticular inflammation in collaboration with other pro-inflammatory cytokines[21]. Although the size of the study limits its generalization, these results may indicate that when IL-1 inhibitors are not effective, switching to an IL-6 inhibitor may be a good option, particularly in patients with extensive joint involvement. Further investigation on this topic is needed. Patients who switched to Tocilizumab due to failure in controlling articular features, were concomitantly treated with Methotrexate. This is in accordance with the 2021 ACR guidelines for the treatment of systemic JIA, that recommend conventional synthetic DMARDs in combination with bDMARDs for children with prominent arthritis[16].

In the other subtypes of JIA, TNFα inhibitors were the most used bDMARDs. Although each of these subtypes probably has a specific pathophysiology, they distinguish from systemic JIA by being more consistent with an autoimmune disease rather than an autoinflammatory disease. In systemic JIA the innate immune system mainly involved, as opposed to the other subtypes which are mostly dictated by the adaptative immune system; the main inflammatory cytokines involved in the pathophysiology of these subtypes are similar - TNFα, IL17, IFNγ and IL23. In systemic JIA, the main inflammatory cytokines are IL1, IL6, IL18, IL32, LRG and ADA2[7]. This may explain why IL1 and IL6 inhibitors are more effective in systemic JIA and TNFα inhibitors are more effective in the other subtypes. Nevertheless, other bDMARDs such as Tocilizumab, Abatacept and Rituximab have also shown clinical efficacy in patients with non-systemic JIA, particularly in polyarthritis and oligoarthritis[16,22,23]. In these subtypes, in the absence of randomized controlled trials, ACR guidelines for treatment of JIA do not recommend any preferred agent, stating that all bDMARDs with proven efficacy are valid options[16,23]. In psoriatic JIA and in enthesitis-related arthritis, TNF inhibitors are the preferred bDMARD class[23,24]. In the study population, all non-systemic JIA patients started with TNF inhibitors, mostly adalimumab. In fact, although other drugs have proven effective, TNF inhibitors remain the most commonly used bDMARDs in children[16], probably because as the first approved bDMARDs in JIA treatment, there is a relatively large amount of data regarding the long-term safety and efficacy in JIA patients, especially with adalimumab and etanercept[25,26]. In our study population, the proportion of patients with enthesis-related arthritis and patients with psoriatic arthritis was higher than in other populations of patients under bDMARDs in literature. In previous studies, the percentage of patients with enthesis-related arthritis treated with bDMARDs ranges between 11% and 16%, and psoriatic arthritis ranges between 4% and 6%[27,28,29,30]. Typically, the proportion of patients with oligoarthritis treated with bDMARDs exceeds that of these two subtypes, contrary to our study population. While we have not encountered a definitive explanation for this, the fact that our unit encompasses both pediatric and young adult rheumatology could account for the higher proportion of these two subtypes, which are more prevalent in adolescents and young adults[31,32]. However, it is unlikely that this has influenced the results of our study, given that a previous retrospective cohort study that analyzed the attainment of inactive disease status after starting TNF-α inhibitors reported that 54% of patients achieved inactive disease status during the 1-year follow up[33], which is consistent with our results.

Most patients with non-systemic JIA received Methotrexate in addition to bDMARD therapy until the end of the follow-up. In fact, methotrexate is the preferred conventional synthetic DMARD (csDMARD), given the vast evidence showing its long-term safety and efficacy in children[34,35,36]. ACR guidelines for the treatment of JIA recommended combination therapy with a csDMARD over biologic monotherapy for patients with polyarticular JIA initiating biologics, for additional disease control[16]. For oligoarticular JIA, evidence favors concomitant bDMARD and csDMARD but suggests that csDMARDs may be tapered off once disease control is attained on a TNF inhibitor, although there is large practice variation regarding when to stop the DMARD[37]. Patients who did not receive methotrexate, mostly had enthesis-related arthritis. Although methotrexate is first-line therapy for children with other categories of JIA, it has not shown to be effective for children with axial disease. However, it has utility for peripheral arthritis in children with enthesis-related arthritis[38].

In our study population, withdrawal was attempted in five patients with long-term inactive disease. Evidence suggests that, in some patients, it may be possible to maintain inactive disease status after discontinuation of bDMARDs. It is, however, unclear how soon after achievement of inactive disease these can be tapered[16]. A systematic review on treatment withdrawal following remission in JIA patients suggests that, overall, disease flares are common after stopping bDMARD therapies, 37% after 8 months and 60–83% after 12 months, which is consistent with our findings[39]. Despite the small number of patients in whom withdrawal was attempted, our findings suggest that two years of inactive disease may be too soon to discontinue these drugs. Additionally, some evidence suggests that physician's opinion, even when based on validated criteria, might not suffice to reliably forecast the successful discontinuation of bDMARD therapy[40]. This is also suggested by our findings, since three of the five patients in whom withdrawal was attempted had to reintroduce

the therapy due to flares shortly after discontinuation. Biological and imaging biomarkers of subclinical inflammation have been studied as potential predictors of flare after withdrawal[41,42,43]. A biomarker-guided strategy in the decision-making process of therapy withdrawal, based in S100A12 and high-sensitivity CPR levels, was studied in the PREVENT-JIA trial and resulted in fewer flares and longer time to the first flare after discontinuation[44]. Other factors associated with increased risks of flare haven´t been consistently identified[45]. However, a recent study by Kearsley-Fleet *et al.* suggests that absence of uveitis, treatment with Tocilizumab (vs Etanercept) and starting biologics early in the course of the disease are associated with successful cessation of bDMARD therapy[39]. Our findings appear to align with this study, as there was only history of uveitis in one patient within the group of patients who flared after withdrawal, and the time until initiation biological therapy was longer in those who experienced relapse. Additionally, our results indicate that ANA-positive patients may have an increased flare risk. In a previous study, a significant difference in flare rates was observed between ANA-positive and ANA-negative patients, with 48 out of 71 ANA-positive patients experiencing flares, compared to 18 out of 39 ANA-negative patients ($p= 0,0047$)[46]. However, some other studies found no association between ANA status and maintenance of inactive disease after treatment withdrawal[30,47,48]. Future studies are needed to substantiate these findings.

The results of the present study also demonstrated the safety of these drugs. Although mild adverse effects were relatively common, serious adverse effects were rare and reversed with drug discontinuation, except for the hypogammaglobulinemia secondary to Rituximab, that is persistent and still requires replacement therapy with human immunoglobulin. Hepatitis in patients receiving anakinra has been previously reported in literature[49]. Membranoproliferative glomerulonephritis in patients receiving TNF inhibitors[50] and persistent hypogammaglobulinemia secondary to Rituximab in JIA patients have also been described[51].

This retrospective cohort study allows for a better comprehension of the current practice in bDMARD therapy, by summarizing patient characteristics and pharmacological treatment in a Portuguese tertiary hospital over five years. There are, however, important limitations to address. First, there may have been a follow-up bias, acknowledging the patients for whom there is missing data – these patients miss appointments the most and may not comply with therapy, which may overestimate our results on therapy effectiveness. Additionally, the small study population may compromise its external validity. Nevertheless, it's important to consider that bDMARD therapy is used mainly as a second or third-line option, which accounts for low numbers of patients. Also, there are limitations inherent to the retrospective design of the study. For example, composite clinical outcome measures, such as the Juvenile Arthritis Disease Activity Score (JADAS)[52], could not be used to assess the therapy effectiveness because a parent global assessment of well-being, measured on a 0-10 visual analog scale (VAS), which was not available in all patients, is necessary to calculate this score.

In conclusion, JIA is a heterogeneous group of diseases with distinct pathophysiological characteristics. The most effective bDMARDs for each JIA subtype are in line with these pathophysiological differences. These diseases may have a severe course and are associated with multiple complications, but the introduction of bDMARDs, which are effective and have an acceptable safety profile, markedly revolutionized the clinical outcome for these patients. However, despite the established efficacy of bDMARDS, further research is needed regarding which specific drug should be used, given different disease features and patient characteristics.

REFERENCES

1. Ravelli A, Martini A. Juvenile Idiopathic Arthritis. Lancet. 2007; 369:767–778.
2. Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology Classification of Ju- venile Idiopathic Arthritis: Second Revision, Edmonton. 2001. J Rheumatol. 2004; 31: 390-392.
3. Duurland CL, Wedderburn LR. Current developments in the use of biomarkers for juvenile idiopathic arthritis. Curr Rheumatol Rep. 2014; 16:406.
4. Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. J Rheumatol 1995; 22:1566.
5. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis in the biologic age. Rheum Dis Clin North Am 2013; 39: 751-766.
6. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis: a revolution in care. Pediatr Rheumatol Online J 2014; 12: 13.
7. Zaripova LN, Midgley A, Christmas SE, Beresford MW, Baildam EM, Oldershaw R A. Juvenile idiopathic arthritis: from aetiopathogenesis to therapeutic approaches. Pediatric Rheumatology. Published Online First: August 2021. doi: 10.1186/s12969-021-00629-8
8. McDonagh JE, Tattersall RS. Adolescent and young adult rheumatology in clinical practice. 2019.
9. Guzman J, Oen K, Tucker LB, et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis 2015; 74: 1854-1860.
10. Muzaffer MA, Dayer JM, Feldman BM, et al. Differences in the profiles of circulating levels of soluble tumor necrosis factor receptors and interleukin 1 receptor antagonist reflect the heterogeneity of the subgroups of juvenile rheumatoid arthritis. J Rheumatol 2002; 29:1071.
11. de Benedetti F, Massa M, Robbioni P, et al. Correlation of serum interleukin-6 levels with joint involvement and thrombocytosis in systemic juvenile rheumatoid arthritis. Arthritis Rheum 1991; 34:1158.
12. Quartier P, Allantaz F, Cimaz R, et al. A multicentre, randomised,

double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. Published Online First: 2011; doi:10.1136/ard.2010.134254
13. Cortis E, Insalaco A. Macrophage activation syndrome in juvenile idiopathic arthritis. Acta Paediatrica (Oslo, Norway: 1992). Supplement, Published Online First: July 2016. doi: 10.1080/08035320600649713.
14. Wallace CA, Huang B, Bandeira M, Ravelli A, Giannini EH. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis & Rheumatism, 52(11), pp.3554–3562.
15. Toplak N, Blazina Š, Avčin T. The role of IL-1 inhibition in systemic juvenile idiopathic arthritis: current status and future perspectives. Drug Des Devel Ther. 2018; 12:1633-1643. Published Online First: 8 Jun 2018. doi:10.2147/DDDT.S114532
16. Onel K, Horton D, Lovell D, et al. 2021 American College of Rheumatology Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Oligoarthritis, Temporomandibular Joint Arthritis, and Systemic Juvenile Idiopathic Arthritis. Arthritis & Rheumatology, Published Online First: 1 March 2022. doi:10.1002/acr.24853
17. Systemic juvenile idiopathic arthritis: Treatment. January 2023. https://www.uptodate.com/contents/systemic-juvenile-idiopathic-arthritis-treatment?search=systemic%20JIA%20treatment&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H12929729. Accessed at February 2023.
18. Hinze CH, Holzinger D, Lainka E, et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J. 2018;16(1):7. Published Online First: 2018 Jan 22. doi:10.1186/s12969-018-0224-2
19. Ter Haar NM, van Dijkhuizen EHP, Swart JF, et al. Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study. Arthritis Rheumatol 2019; 71:1163.
20. Quartier P, Allantaz F, Cimaz R, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Rheum, A. Extended report. Dis, Published Online First: 20 December 2010. doi: 10.1136/ard.2010.134254
21. Akioka S. Interleukin-6 in juvenile idiopathic arthritis. Modern Rheumatology, 29(2), Published Online First: March 2019. doi: 10.1080/14397595.2019.1574697.
22. Polyarticular juvenile idiopathic arthritis: Treatment. January. 2022. https://www.uptodate.com/contents/polyarticular-juvenile-idiopathic-arthritis-treatment?search=JIA%20threatment&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H9390825. Accessed: 19 Mar. 2023
23. Ringold S, Angeles-Han ST, Beukelman T, 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 Care & Research, Published Online First: 25 April 2019. doi: 10.1002/art.40884
24. Psoriatic juvenile idiopathic arthritis: Management and prognosis. November 2022. https://www.uptodate.com/contents/psoriatic-juvenile-idiopathic-arthritis-management-and-prognosis?search=psoriatic%20jia%20treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed: 19 Mar. 2023.
25. Klotsche J, Niewerth M, Haas JP, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Annals of the Rheumatic Diseases, 75(5), Published First Online: April 2019. doi: 10.1136/annrheumdis-annrheumdis-2014-206747
26. Giannini EH, Ilowite NT, Lovell DJ, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum 2009; 60:2794.
27. Baszis K, Garbutt J, Toib D, Mao J, King A, White A, et al. Clinical outcomes after withdrawal of anti-tumor necrosis factor alpha therapy in patients with juvenile idiopathic arthritis: a twelve-year experience. Arthritis Rheum. 2011;63(10):3163–8.
28. Kearsley-Fleet L, Baildam E, Beresford MW, Douglas S, Foster HE, Southwood TR, Hyrich KL, Ciurtin C. Successful stopping of biologic therapy for remission in children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford). 2023 May 2;62(5):1926-1935. doi: 10.1093/rheumatology/keac463. PMID: 36104094; PMCID: PMC10152290.
29. Nieto-González, J.C., Trives-Folguera, L., Melgarejo-Ortuño, A. et al. Persistence and adherence to biologic therapies in juvenile idiopathic arthritis. Sci Rep 11, 16195 (2021). https://doi.org/10.1038/s41598-021-95252-8
30. Simonini G, Ferrara G, Pontikaki I, Scoccimarro E, Giani T, Taddio A, et al. Flares after withdrawal of biologic therapies in juvenile idiopathic arthri- tis: clinical and laboratory correlates of remission duration. Arthritis Care Res (Hoboken). 2018;70(7):1046–51.
31. Weiss P. Diagnosis and treatment of enthesitis-related arthritis. Adolesc Health Med Ther. 2012;3:67-74 https://doi.org/10.2147/AHMT.S25872
32. Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. Arthritis Rheum. 2006 Nov;54(11):3564-72. doi: 10.1002/art.22173. PMID: 17075862.
33. Donnithorne KJ, Cron RQ, Beukelman T. Attainment of inactive disease status following initiation of TNF-α inhibitor therapy for juvenile idiopathic arthritis: enthesitis-related arthritis predicts persistent active disease. J Rheumatol. 2011;38(12):2675-2681. doi:10.3899/jrheum.110427
34. Ravelli A, Davi S, Bracciolini G, et al. Intra-articular corticosteroids versus intra-articular corticosteroids plus methotrexate in oligoarticular juvenile idiopathic arthritis: a multicentre, prospective, randomised, open-label trial. Lancet 2017; 389:909–916.
35. Albarouni M, Becker I, Horneff G. Predictors of response to methotrexate in juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2014; 12:35.
36. Bava C, Mongelli F, Pistorio A, et al. A prediction rule for lack of achievement of inactive disease with methotrexate as the sole disease-modifying antirheumatic therapy in juvenile idiopathic arthritis. Pediatr Rheumatol Online J 2019; 17:50.
37. Polyarticular juvenile idiopathic arthritis: Treatment. January. 2022. https://www.uptodate.com/contents/polyarticular-juvenile-idiopathic-arthritis-treatment?search=JIA%20threatment&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H9390825. Accessed: 19 Mar. 2023
38. Spondyloarthritis in children. Feb 2022. https://www.uptodate.com/contents/spondyloarthritis-in-children?search=enthesitis%20related%20arthritis&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H13 Accessed in 19 Mar. 2023.
39. Gieling, J., van den Bemt, B., Hoppenreijs, E., & Schatorjé, E. (2022). Discontinuation of biologic DMARDs in non-systemic JIA patients: a scoping review of relapse rates and associated factors. Pediatric Rheumatology, 20(1). https://doi.org/10.1186/

s12969-022-00769-5
40. Kearsley-Fleet L, Baildam E, Beresford MW, Douglas S, Foster HE, Southwood TR, Hyrich KL, Ciurtin C. Successful stopping of biologic therapy for remission in children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford). 2023 May 2;62(5):1926-1935. doi: 10.1093/rheumatology/keac463. PMID: 36104094; PMCID: PMC10152290.
41. Anink J, Van Suijlekom-Smit LWA, Otten MH. et al. MRP8/14 serum levels as a predictor of response to starting and stopping anti-TNF treatment in juvenile idiopathic arthritis. Arthritis Res Ther 2015;17:200.
42. Panwar J, Tolend M, Redd B. et al. Consensus-driven conceptual development of a standardized whole body-MRI scoring system for assessment of disease activity in juvenile idiopathic arthritis: MRI in JIA OMERACT working group. Semin Arthritis Rheum 2021;51:1350–9.
43. Wang C, Qin Y, Xu J. et al. Correlation of ultrasound synovitis joint count with disease activity and its longitudinal variation with treatment response to etanercept in rheumatoid arthritis. Ultrasound Med Biol 2021;47:2543–9.
44. Gerss J, Tedy M, Klein A. et al. Prevention of disease flares by risk-adapted stratification of therapy withdrawal in juvenile idiopathic arthritis: results from the PREVENT-JIA trial. Ann Rheum Dis 2022;81:990–7.
45. Halyabar O, Mehta J, Ringold S, Rumsey DG, Horton DB. Treatment Withdrawal Following Remission in Juvenile Idiopathic Arthritis: A Systematic Review of the Literature. Pediatric Drugs, 21(6), pp.469–492.
46. Aquilani A, Marafon DP, Marasco E, Nicolai R, Messia V, Perfetti F, et al. Predictors of flare following etanercept withdrawal in patients with rheumatoid factor-negative juvenile idiopathic arthritis who reached remission while taking medication. J Rheumatol. 2018;45(7):956–61.
47. Lovell DJ, Johnson AL, Huang B, Gottlieb BS, Morris PW, Kimura Y, et al. Risk, timing, and predictors of disease flare after discontinuation of anti-tumor necrosis factor therapy in children with polyarticular forms of juvenile idiopathic arthritis with clinically inactive disease. Arthritis Rheumatol. 2018;70(9):1508–18.
48. Iglesias E, Torrente-Segarra V, Bou R, Ricart S, Gonzalez MI, Sanchez J, et al. Non-systemic juvenile idiopathic arthritis outcome after reaching clinical remission with anti-TNF-alpha therapy: a clinical practice obser- vational study of patients who discontinued treatment. Rheumatol Int. 2014;34(8):1053–7.
49. Wikén M, Hallén B, Kullenberg T, Koskinen LO. Development and effect of antibodies to anakinra during treatment of severe CAPS: sub-analysis of a long-term safety and efficacy study. Clinical Rheumatology, Published Online First: Jul 2018. doi: 10.1007/s10067-018-4196-x.
50. Stokes MB, Foster K, Markowitz GS, et al. Development of glomerulonephritis during anti-TNF-α therapy for rheumatoid arthritis. Nephrology Dialysis Transplantation, Published Online First: April 2005. doi: 10.1093/ndt/gfh832.
51. Reis J, Aguiar F, Brito I. Anti CD20 (Rituximab) therapy in refractory pediatric rheumatic diseases. Acta Rheumatol Port. 2016; 41: 45-55
52. Consolaro A, Giancane G, Schiappapietra B, et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatr Rheumatol, Published Online First: 18 April 2016. doi: 10.1186/s12969-016-0085-5