







## Review

# Patterns and determinants of response to novel therapies in juvenile and adult-onset polyarthritis

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## Abstract

Biologic and targeted synthetic DMARDs (b/tsDMARDs) have revolutionized the management of multiple rheumatic inflammatory conditions. Among these, polyarticular JIA (pJIA) and RA display similarities in terms of disease pathophysiology and response pattern to b/tsDMARDs. Indeed, the therapeutic efficacy of novel targeted drugs is variable among individual patients, in both RA and pJIA. The mechanisms and determinants of this heterogeneous response are diverse and complex, such that the development of true ‘precision’-medicine strategies has proven highly challenging. In this review, we will discuss pathophysiological, patient-specific, drug-specific and environmental factors contributing to individual therapeutic response in pJIA in comparison with what is known in RA. Although some biomarkers have been identified that stratify with respect to the likelihood of either therapeutic response or non-response, few have proved useful in clinical practice so far, likely due to the complexity of treatment-response mechanisms. Consequently, we propose a pragmatic, patient-centred and clinically based approach, i.e. personalized instead of biomarker-based precision medicine in JIA.

**Keywords:** rheumatoid arthritis, juvenile idiopathic arthritis, response to therapy, personalized medicine.

### Rheumatology key messages

- Current targeted DMARDs used in RA and JIA seem equally effective at the group level.
- Individual determinants of response to therapy are complex and multifactorial.
- Personalized care in JIA mostly relies on a clinically based approach.

## Introduction

JIA refers to a heterogeneous group of rheumatic conditions in children, characterized by chronic immune-mediated arthritis of unknown aetiology, and associated with a risk for both short- and long-term morbidity. Biologic and targeted synthetic DMARDs (b/tsDMARDs) have proven to be effective in treating JIA-associated synovitis in randomized control

trials (RCTs). Consequently, their implementation in standard treatment regimens for JIA over the last two decades has dramatically improved disease outcomes [1]. Nevertheless, evidence has accrued that the efficacy of distinct b/tsDMARDs is heterogeneous across and also within JIA subtypes and may change during the patient’s disease course [2–4].

Polyarticular JIA (accounting for ~20% of JIA patients) refers more to a clinical course than to a single entity. It comprises RF-positive and RF-negative subsets. Even within those subgroups, heterogeneity prevails: for instance, ANA-positive polyarticular JIA with early onset likely represents a pathophysiological continuum with ANA-positive oligoarticular JIA, including a risk for chronic uveitis [5, 6]. pJIA and RA appear to be (at the very least) closely related conditions, as they bear a number of similarities in terms of clinical features, genetic risk factors, synovial pathology, and response to targeted therapies [5, 7, 8].

Thus, the drug armamentarium and therapeutic approach in pJIA is largely modelled on data from RA. MTX is the first-line systemic therapy recommended in both conditions. Failure to achieve timely clinical treatment objectives requires therapeutic adaptation, including the use of b/tsDMARDs in the two conditions (treat-to-target strategy). b/tsDMARDs are molecules targeted against key players in synovial inflammation: cytokines or their receptor (TNF $\alpha$ , IL6R), costimulatory molecules (CD80/86) or downstream signalling proteins [Janus kinases (JAKs)]. A notable exception is rituximab (anti-CD20 antibody), which has never been tested in a RCT for pJIA but might be effective according to observational data [9]. In both disease phenotypes, individual response to a specific therapy is highly variable: while some patients will display good response to first-line therapy, others will be switched from one targeted drug to another, sometimes with limited clinical benefit [2, 10–15].

Determinants of the diverse and variable therapeutic response among patients with chronic arthritis across the age spectrum have only been partially elucidated. Thus, prediction of response in individual patients remains a distant dream for clinicians who are to make therapeutic choices from the increasingly available drug armamentarium. Nevertheless, several hypotheses are emerging to provide biological explanations for the heterogeneity in therapeutic responses to b/tsDMARDs. In this review, we will highlight the major players and pathways involved in the pathophysiology of chronic synovitis and describe the observed response patterns to b/tsDMARDs in both pJIA and RA. We will then review the factors known to influence the treatment response

in RA, and discuss their potential relevance for pJIA. Finally, we will discuss the lessons, limits and challenges relating to biomarkers-based approaches aiming at response prediction.

## Pathophysiology of synovitis in pJIA and similarities with RA

JIA pathogenesis has been recently reviewed in detail [16]. We will briefly review the key findings, with a focus on features shared between pJIA and RA pathology (Table 1) [7, 16–33].

The genesis of pJIA is dependent on a complex process involving the interaction between genetic [such as specific MHCII alleles or single nucleotide polymorphisms (SNPs) in *PTPN2*], sex-related and environmental factors. How individual risk factors ultimately result in immune-mediated arthritis remains widely unknown. The observed immune response includes coordinated activation of innate and adaptive immune effectors. More specifically, activated CD4<sup>+</sup> T cells (expressing Th1/Th17 inflammatory cytokines and T peripheral helpers) [17, 18], B cells [34], and macrophages likely play key roles at the established phase of synovial inflammation [35], while Tregs seem to be impaired [19, 21]. Cross-talk between different effector cells relies on cytokines and costimulatory molecules, the expression of which is dysregulated in pJIA [20, 21]. It is unclear why the dysregulated immune response is specifically directed toward synovial tissue, but oligoclonality of synovial T cells suggests a role of local neo/auto-antigen recognition [36]. In RA, joint-resident cells [fibroblast-like synoviocytes (FLSs), resident macrophages and resident memory T cells) and their cross-talk with immune cells have been involved in disease pathophysiology [17, 18, 34, 37, 38]. The co-existence of several immune and resident cell subsets/states in RA synovitis is being unravelled using single-cell technologies [39, 40]. Whether similar findings are reproducible in pJIA remains to be determined.

Currently it is unclear whether all pJIA patients share a single pathogenic process or whether inter-individual variations exist in the involvement/activation of specific pathogenic players, also within a distinct seemingly 'homogeneous' subtype (e.g. seropositive pJIA). As an example, considering a pJIA patient resistant to TNF blockade therapy, one could question

**Table 1.** Key selected features shared in RA and pJIA pathophysiology

		References
Genetic background	Association with HLADRB1.04 allele for seropositive disease	[7, 25]
	Association with Gly at position 13 in HLA-DRB1.13 for seronegative disease	[7, 25]
	Association with <i>PTPN22</i> and <i>STAT1/STAT4</i> polymorphisms	[7, 25]
Synovial pathology	Clonally expanded CD8 T cells in SF	[26]
	Presence of Th1 and Th17 cells in SF	[17, 27–29]
	Variable lymphoid neogenesis and plasma cell infiltration in synovial tissue	[24, 30]
	Joint accumulation of peripheral T helper cells (CD4 <sup>+</sup> IL-21 <sup>+</sup> )	[18, 31]
	Similar effector Treg profiles in SF	[32]
	Synovial T and B cell infiltrates	[23]
Circulating factors	RF and/or ACPA positivity in a subset of patients	
	Circulating pathogenic-like CD4 <sup>+</sup> T cell signature sharing similar phenotype (and associated with disease activity)	[33]
	TNF $\alpha$ and IL6 signature	[20, 21]
Response to targeted therapies	Increased levels of inflammation-associated T-reg	[19]
	TNF $\alpha$ blockade	[16, 22]
	IL6R blockade	
	CTLA4Ig	
	JAK inhibition	

pJIA: polyarticular JIA.

whether this is the result of a TNF $\alpha$ -independent disease or, in contrast, of excessive TNF $\alpha$  production overwhelming therapy. bDMARD and tsDMARD therapies used to treat pJIA specifically target a number of effector molecules downstream in this pathophysiological process. Notably, these drugs reportedly are also effective in treating RA-associated synovitis, other inflammatory arthritis and non-articular immune-mediated conditions [41]. Overall, current targeted bDMARDs and tsDMARDs used both in RA and pJIA block downstream inflammatory mechanisms rather than disease-specific processes [16]. Consequently, increased infection susceptibility is an expected side-effect of these agents [42].

In addition to these targeted drugs, other therapeutic agents with broader impacts on the immune system (systemic and local glucocorticoids), or with lesser known mechanisms of action (MTX), continue to be widely used. In very few patients with severe refractory JIA, autologous or allogenic stem cell transplantations have been used to ‘reset’ the immune system, with uncertain risk/benefit balance [43, 44]. Other approaches aiming to restore immune tolerance are at the experimental stage [45].

## Measuring disease activity and response to therapy in pJIA

Currently, the tools used to measure clinical disease activity and treatment response in pJIA are similar to those used in RA: composite scores compiling objective (number of joints with active arthritis, ESR, CRP) and subjective (patients’/parents’ or physicians’ global assessment of pain, well-being and disease activity) components (reviewed in [16]). Two caveats regarding the reliability of these composite scores are (i) differentiation between active disease and damage can be challenging, and (ii) the relationships between inflammation, pain, and their physical or psychological consequences are not fully understood [46]. Another layer of complexity in disease activity assessment results from the existence of extra-articular inflammation, especially uveitis. Objective measures are also not free of limitations: in RA, both

IL6R inhibitors and JAK inhibitors (JAKis) reportedly have greater effects on acute-phase reactants than other bDMARDs, potentially independent of improvement in other clinical indices in some patients [47–49].

Longitudinal measures of disease activity enable the evaluation of treatment effects over time [50–52]. The ACR pediatric criteria for improvement are the current gold standard for assessing treatment response [53]. Depending on the criteria used, treatment response will be expressed as a relative improvement (e.g. ACR pedi 30), an absolute reduction in disease activity [e.g. change in the 10-joints Juvenile Arthritis Disease Activity Score ( $\Delta$ JADAS10)] [52], or the achievement of a certain threshold (e.g. JADAS10 minimal disease activity) [54]. Focusing on one or the other might impact the results of clinical trials [47]. Furthermore, the state of response to therapy is not permanent, as secondary loss of response early or later in the therapy course is a well-known phenomenon in both JIA and RA [55–57]. Overall, the complexity of assessing treatment effects should not be underestimated.

## Response to specific targeted therapies: insights from RA

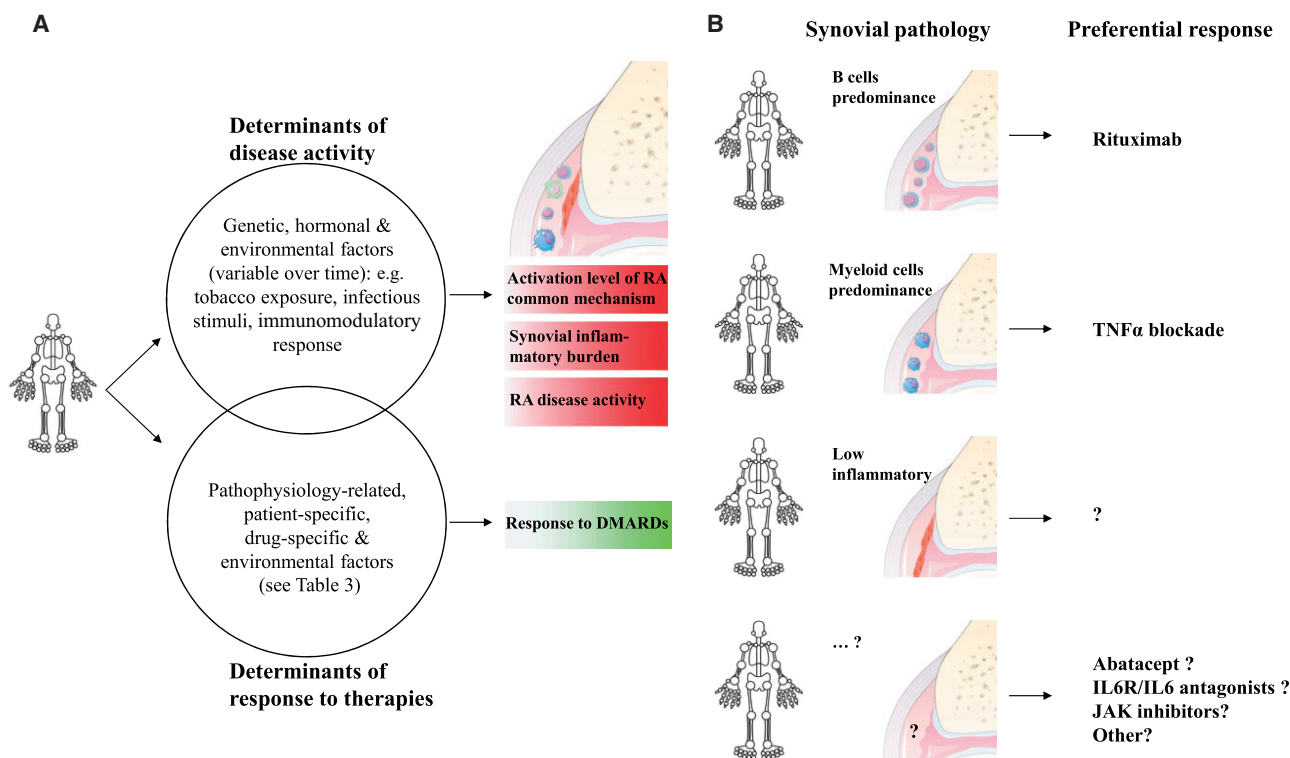
The disparate effect of b/tsDMARDs therapies observed in RA may have several biological explanations, and these have been listed in Table 2 [4, 13, 22, 40, 55, 58–94]. We will discuss in the following paragraphs pathophysiological, patient-specific, drug-specific and environmental factors modulating treatment response in RA.

Many authors consider that all RA patients share common core pathophysiological mechanisms that can (at least partially) be modulated by therapies [22, 95, 96] (Fig. 1A). Analysis of treatment responses at the group level in RCTs in RA reveals a striking prototypical pattern, sometimes called the ‘60–40–20 rule’. Thus, among MTX-resistant patients starting the first b/tsDMARDs, 60% will have a limited response (ACR20), 40% a moderate response (ACR50) and

**Table 2.** Possible mechanisms occurring in primary and secondary non-response to therapy in RA and JIA

Primary non-response to treatment	RA	JIA
<b>Pathophysiology-related factors</b>		
Common core pathway with a severity spectrum	[13, 22, 40, 58]	[81, 82]
Existence of distinct arthritis subtypes with different pathogenic mechanisms (endotypes)	[59–61]	[80]
Disease-stage at treatment start (including window-of-opportunity concept)	[62]	[73, 74, 78]
<b>Patient-specific factors</b>		
Genetic polymorphisms (affecting disease mechanisms or drug metabolism or modifying target of therapies), post-translational modifications modifying epitope on targeted cytokines	[63, 64]	[76, 77, 83]
Epigenetic factors	[84, 85]	[86]
Comorbidities: smoking, obesity, non-adherence to treatment, etc.	[65–67, 87]	[4, 75, 79, 88]
Sex	[89]	
<b>Environmental factors</b>		
Microbiota, infectious exposure, etc.	[90]	
<b>Drug-specific factors</b>		
Pharmacodynamic factors (drug dose, half-life, metabolism/recycling, albumin concentration etc.)	[70]	[91]
Pharmacologic factors (binding epitopes, affinity, activation of antibody-dependent cell-mediated toxicity, distribution in inflamed tissue, off-target effects)	[68, 69, 92]	[68, 69]
Concomitant (synergic effect, e.g. ledeftrexate and TNF inhibitors) or previous therapies	[93, 94]	[55]
<b>Secondary non-response to treatment</b>	<b>RA</b>	<b>JIA</b>
Anti-drug antibodies against bDMARDs	[71, 72]	[55]
Activation of ‘escape’ pathways		

bDMARD: biologic DMARD.



**Figure 1.** Schematic representation of the main hypothetical models to explain heterogeneity in response to therapies in RA. Common pathway model in (A); endotypes in (B)

20% will be good responders (ACR70) after 6 months of therapy [22, 96–98]. Although not based on head-to-head trials, this observation seems to hold true regardless of the therapeutic target of the drug used (TNF $\alpha$ , CD20<sup>+</sup> cells, IL6R, CD80/CD28, or JAK enzymes). Recent meta-analyses of RCTs including >9000 patients and findings from registry data from >30 000 patients confirmed this seemingly similar efficacy of most current b/tsDMARDs at the group level [99, 100]. Accordingly, the 2022 updated EULAR recommendations do not propose the use of one molecule over the other after MTX failure [101]. The ‘60–40–20 rule’ led to the hypothesis that all current therapies act on the same common downstream processes (the so-called common pathway hypothesis), despite their disparate primary targets [22]. In keeping with this hypothesis, by comparing 50 pairs of synovial biopsy transcriptomic patterns before and after therapy, we found that five different DMARDs induced a similar coordinated inhibition of both lymphoid and myeloid activation pathways in RA synovium, despite having different primary targets [102]. According to the common pathway hypothesis, disease activity in an individual patient would be determined by the level of activation of this common downstream pathway (and its modulation by immune regulatory mechanisms) [40, 58], and response to a specific drug would be determined by several additional factors (see Table 2). Eventually, refractory disease would arise from the inability of DMARDs to suppress the excessive activation of this core process [11, 58] (Fig. 1A). The existence of multiple targetable effectors in this common pathway raises the question of combination therapy in refractory RA. However, caution is warranted in view of the potentially increased risk of infection [103, 104].

Another hypothesis to account for heterogeneous b/tsDMARD effects relates to the co-existence of several

endotypes under the umbrella term of RA. The notion of endotypes refers to subgroups of patients displaying differences in pathogenic mechanisms while having the same clinical phenotype. It is generally accepted that these ‘endotypic’ differences may result in different therapeutic responsiveness [105, 106]. Thus, pathophysiology in individuals with RA could be driven by different key players: some patients could have a predominantly TNF $\alpha$ -driven disease, others a B cell- or T cell-dependent disease, determining their response to therapies targeting those different effectors [59, 107, 108] (Fig. 1B). Numerous studies on synovial tissue have supported this hypothesis by showing that the composition of the RA synovium displays a high level of heterogeneity: the relative presence of T cells, B cells, and myeloid cells, and the levels of expression of several cytokines vary widely between patients [59, 60, 109, 110]. According to their synovial pathology pattern, individuals with RA could thus be classified into different pathotypes [60]. These observations have yielded enthusiasm for identifying precision medicine applications, as recently explored in a pilot study [61]. However, although highly attractive, the hypothesis of different ‘endotypes’ existing within the diagnosis of RA faces several criticisms, based on both clinical observation and pathophysiological considerations.

First, patients failing an initial TNF $\alpha$  inhibitor have an equal chance of responding to (i) a second TNF $\alpha$  inhibitor or (ii) a bDMARD with a different target [111–113]. A recent study also showed that after failing the first JAKi, cycling to another JAKi and switching to another bDMARD appear to have similar effectiveness [114]. These observations are reflected in recent EULAR recommendations that do not propose a class switch after primary failure of a first biologic DMARD [101]. Another observation argues against the



existence of endotypes: the more therapies for which a patient fails to achieve a clinical response, the less likely they are to respond to the following ones. This points towards the concept of disease severity rather than to distinct endotypes as a cause of poor response to therapy [13, 22]. Next, the preferential activation of a single cell type or pathway, independent of others, does not fit with the high interdependency of all effectors in RA pathobiology [13, 95, 115]. Furthermore, it remains unclear whether the observed heterogeneity in synovial tissue patterns points to intrinsic biological differences between patients, to different stages of the same process, or is influenced by other factors (such as disease duration, disease activity or ongoing therapies) [58, 102, 106, 116, 117]. Thus, we have shown that clinical disease activity (and not distinct pathotypes) is the major driver of transcriptomic heterogeneity in the synovia of a large cohort of untreated early RA patients [118]. Although it remains plausible that the synovial representation of a drug target at least partially determines its clinical effect, many other factors influence individual response to therapy, as we will discuss in the following paragraphs (Table 2).

Another potentially critical determinant factor for treatment response may be the time of active disease before starting a therapy, as supported by extensive clinical observation [62, 119, 120]. The underlying hypothesis is that early achievement of disease control would lead to a more favourable disease course in the future. This has led to the notion of ‘window of opportunity’, with critical implications in the therapeutic (development of treat-to-target strategies, early use of steroids, etc.) and research fields (remission-induction protocols with bDMARDs and step-down approaches). Importantly, evidence that management during this early period will impact the disease course in the very long term is still scarce [62]. Furthermore, a biological basis for the ‘window of opportunity’ is not yet confirmed, but probably involves long-term imprinting (e.g. through epigenetic modifications) of pathogenic cell types under protracted stimulation [121]. From a broader point of view, a dynamic pathophysiological process in RA could suggest that different phases of the disease are characterized by increased susceptibility to specific therapies, although no available evidence currently corroborates this hypothesis [122, 123].

In addition to the above-mentioned factors related to RA pathological processes, a variety of other patient-specific, drug-specific and environment determinants (listed in Table 2) can influence response to therapies. Genetic polymorphisms have been associated with treatment response/resistance in RA (reviewed in [124]). The most frequently reported polymorphisms show an association between *FCGR* genes and response to mAbs, suggesting that variations in FcγR expression/structure could influence drug metabolism and thereby therapeutic effects [63, 64, 125, 126]. The link between *FCGR* polymorphisms and response to biologics is also well described in Crohn’s disease [127]. Associations between polymorphisms in other genes or their promoters (e.g. *TNF*, *TNFR2*, *IL6*, *IL6R*) and the effect of certain bDMARDs have been reported in RA, but few of these observations have been replicated or functionally confirmed [124, 128, 129]. Evidence also links therapeutic response to other external factors such as smoking status, obesity (through pharmacokinetic, immune-metabolic and/or proinflammatory effects of adipose tissue), microbiota or treatment adherence [65–67].

Therapeutic effects observed in RA are also modulated by a number of drug-specific factors. Pharmacological characteristics such as drug dose, systemic drug levels, administration intervals and drug metabolism obviously influence drug effects [130]. bDMARDs targeting the same molecule (e.g. *TNFα*) may display relevant differences in efficacy, related to binding epitopes, affinity, activation of antibody-dependent cell-mediated toxicity, distribution in inflamed tissue, or recycling through to FcRn [68, 69].

Obviously, loss of an initial therapeutic response can arise from the development of anti-drug neutralizing antibodies (ADAbs). How immunization to a particular drug might impact the outcomes of subsequent therapies of drugs with a similar molecular structure (mAbs) is not clear [70–72]. From an intuitive point of view, the distinction between therapeutic failure in the presence or absence of ADAbs seems relevant. Nevertheless, observational data in RA has not suggested any added value of therapeutic monitoring (ADAb-status) as a clue for choosing the subsequent bDMARD (switch to a *TNF* inhibitor *vs* a non-*TNF* inhibitor) after failing of adalimumab therapy [131]. This question is being further investigated in an ongoing RCT [132]. Finally, the activation of potential escape pathways by inflammatory cells under treatment is receiving increasing attention in the field of IBDs but has not (or possibly has not yet) been observed in inflammatory arthritis [127].

## Response to specific targeted therapies in pJIA

MTX is the cornerstone of first-line therapy for pJIA, and adjunctive therapeutic options include NSAIDs, and IA or a limited course of systemic CSs. B/tsDMARDs are used in case of insufficient disease control or intolerance of first-line therapy [16, 73, 133, 134]. The reported rates of first-line therapy failure are variable, but a recent study showed that up to 50% of pJIA patients needed a second-line therapy to achieve recommended disease activity targets during the first year [74]. As for RA, response to targeted therapies in pJIA is widely heterogeneous between individual patients [135].

In contrast to RA, large RCTs studying the efficacy of b/tsDMARDs in children are scarce, often including heterogeneous patient populations in terms of JIA subtype, age, ongoing and previous therapies, etc. (Table 3). Comparative RCTs of different DMARDs have never been conducted in the paediatric population, and no such trial is currently registered on ClinicalTrials.gov.

Nevertheless, analyzing patterns of response to targeted therapies in RCTs and registries can be informative about pJIA pathophysiology (as we have previously shown in RA). Rates of response (achievement of *Pedi* ACR 30 response after 12 weeks of open-label phase) to b/tsDMARDs in the major RCTs for JIA are shown in Fig. 2A [136–145]. The above-mentioned limitations prevent direct comparison across studies, but a picture similar to that observed in RA (all drugs having a comparable clinical efficacy profile at the group level) seems to emerge. This is further supported by real-life data from the BIKER registry, which show strikingly similar responses to etanercept, adalimumab and tocilizumab after 3 months of treatment (Fig. 2B) [75]. The similar efficacy between the three bDMARDs was sustained during 24 months of follow-up. Another striking parallel with RA studies concerns resistance to preceding therapies: failure of response to previous bDMARDs is associated with a reduced chance of

**Table 3.** Baseline clinical characteristics of patients enrolled in main RCT evaluating b/tsDMARD efficacy in JIA

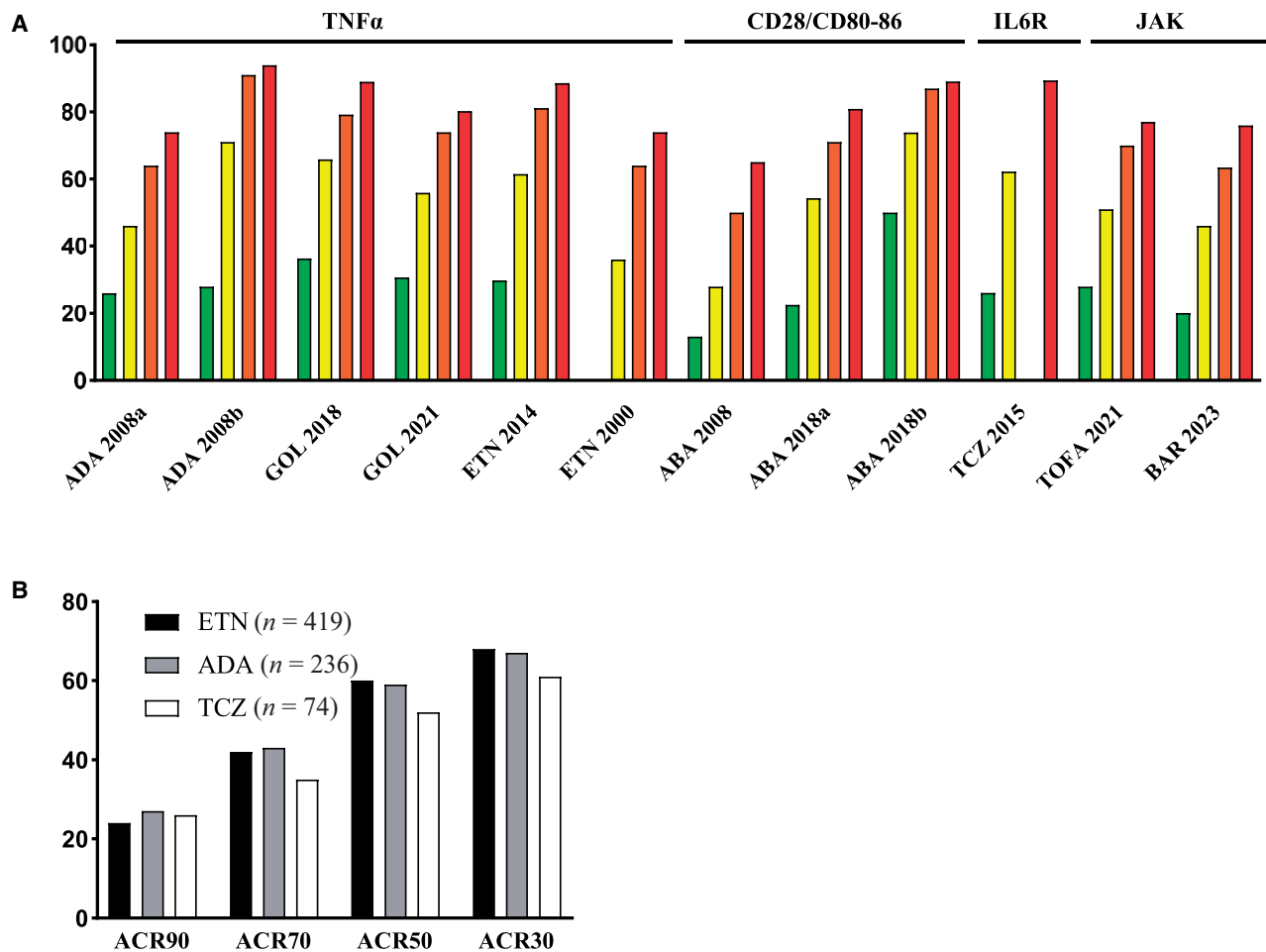
	ADA 2008a (s.c.)	ADA 2008b (s.c.)	GOL 2018 (s.c.)	GOL 2021 (i.v.)	ETN 2014 (s.c.)	ETN 2000 (s.c.)	ABA 2008 (i.v.)	ABA 2018a (s.c.)	ABA 2018b (s.c.)	TCZ 2015 (i.v.)	TOFA 2021 (oral)	BAR 2023 (oral)
Number of patients	86	85	173	127	127	69	190	173	46	188	225	220
Age (years)	11.1 ± 3.8	11.4 ± 3.3	11.2 ± 4.4	13.0 [8.0, 15.0]	11.7 ± 4.5	10.5	12.4 ± 3.0	13.0 [10.0–15.0]	4.0 [3.0–5.0]	11 ± 4.0	13.0 [9.0–15.0]	14.0 [12.0–16.0]
Dose (max)	24 mg/m <sup>2</sup> (40)/2 wk	24 mg/m <sup>2</sup> (40)/2 wk	30 mg/m <sup>2</sup> (50)/4 wk	80 mg/m <sup>2</sup> at wks 0, 4 and 12	0.8 mg/kg/wk	0.4 mg/kg twice a week	10 mg/kg (1 g) (wk 0,2,4,8,12)	10–25 kg: 50 mg/wk 25–50 kg: 87.5 mg/wk >50 kg: 125 mg/wk	10–25 kg: 50 mg/wk 25–50 kg: 87.5 mg/wk >50 kg: 125 mg/wk	<30 kg: 8–10 mg/kg/4 wk >30 kg: 8 mg/kg/4 wk	In two doses: 5–7 kg: 4 mg 7–10 kg: 5 mg 10–15 kg: 6 mg 15–25 kg: 7 mg 25–40 kg: 8 mg >40 kg: 10 mg	9–17 y: 4 mg/d; 2–8 y: 2 mg/d
Disease duration years	3.6 ± 4.0	4.0 ± 3.7	≥0.5	1.4 [0.5–4.0]	2.2 ± 2.2	5.9	4.4 ± 3.8	2 [0.0–4.0]	0.5 [0.0–1.0]	4.2 ± 3.7	2.5 [1.0–5.6]	2.7 [1.0–6.0]
ILAR categories	pJIA <sup>a</sup>	pJIA <sup>a</sup>								pJIA <sup>b</sup>		
OJIA (extended)			12.7%	6.3%	47.2%	10%	14%	11%	21.7%		12.4%	7%
pJIA RF			52%	42.5%	0%	36%	44%	54.3%	63%		46.2%	NA
pJIA RF <sup>+</sup>	21%	23%	19.7%	34.6%	0%	22%	20%	26.6%	6.5%	29%	17.3%	NA
ERA			0%	9.4%	29.9%	0%	0%	2.3%	0%		9.3%	23%
PsJIA			8.7%	3.9%	22.8%	0%	0%	0%	8.7%		8.9%	5%
sJIA			6.9%	3.1%	0%	32%	20%	2.9%	0%		5.7%	0%
Ongoing MTX	0%	100%	100%	100%	67.7%	72% (WO)	73.6%	78.6%	80.4%	79%	65%	58%
Ongoing steroids	NA	NA	24.3%	37%	12.6%	36%	NA	32.4%	19.6%	46%	32%	33%
Prior bDMARD use	0%	0%	12.1%	22.1%	NA	0%	30%	26.6%	21.7%	32%	38%	53%
PhGA (0–100)	58	59.7	56 ± 20	55 [45–68]	50 ± 18	70	54.2	48	50	61.4	60	65 ± 2
SJC	13.2	16.3	15 ± 10 <sup>c</sup>	14 [9–22] <sup>c</sup>	5.5 ± 4.2	28 <sup>c</sup>	16.2 <sup>c</sup>	10 <sup>c</sup>	7 <sup>c</sup>	20.3 <sup>c</sup>	10.0 <sup>c</sup>	12.8 ± 11.1 <sup>c</sup>
TJC	9.5	13.3	15 ± 10 <sup>c</sup>	14 [9–22] <sup>c</sup>	6.4 ± 5.2	28 <sup>c</sup>	16.2 <sup>c</sup>	10 <sup>c</sup>	7 <sup>c</sup>	20.3 <sup>c</sup>	10.0 <sup>c</sup>	12.8 ± 11.1 <sup>c</sup>
CRP (mean or median) (mg/dl)	0.7	0.8	1.1 ± 2.2	0.5 [0.1–1.1]	0.8 ± 1.5	3.5	0.32	0.2	0.1	2.3	0.3	NA
JADAS	NA	NA	25.8	28.4	NA	NA	NA	21	18.1	NA	20.1	21.7 ± 8.8

Values are expressed as percentages or mean ± S.D. or median [interquartile range]. a and b after year represents different populations of the same trial (testing the same drug).

<sup>a</sup> Polyarticular JIA, any type of onset.

<sup>b</sup> Inclusion criteria: RF<sup>+</sup> or RF<sup>−</sup> polyarticular JIA or extended OJIA.

<sup>c</sup> Joint with active arthritis, no specific data on TJC/SJC. bDMARD: biologic DMARD; ERA: enthesitis-related JIA; JADAS: JIA DAS; NA: not available; OJIA: oligoarticular JIA; pJIA: polyarticular JIA; PhGA: Physician Global Assessment; PsJIA: psoriatic Juvenile idiopathic Arthritis; SJC: swollen joint count; sJIA: systemic JIA; TJC: tender joint count; wk: weeks; WO: at washout; tsDMARD: targeted synthetic DMARD; RCT: randomized controlled trial; ABA: abatacept; ADA: adalimumab; BAR, baricitinib; ETN: etanercept; GOL: golimumab; TCZ: tocilizumab; TOFA: tofacitinib.



**Figure 2.** Response to targeted therapies in pJIA. Response rate to b/tsDMARDs during the open-label phase of main RCT or in BIKER registry. **(A)** JIA ACR 30 (red), 50 (orange), 70 (yellow) and 90 (green) in main RCT evaluating b/tsDMARD efficacy in JIA. Response is evaluated after 12 or 18 weeks of open-label phase, depending on the trial design. For TOFA trial, results are shown only for the pJIA population. Trials specific to sJIA are not shown here. Variations between studies must be interpreted with regards to heterogeneous baseline clinical features (see Table 3). **(B)** JIA ACR 30/50/70/90 response rate to etanercept (black), adalimumab (grey) and tocilizumab (white) after 3 months in the BIKER registry. Numbers of patients in each subgroup are shown on the graph. ABA: abatacept; ADA: adalimumab; BAR, baricitinib; ETN: etanercept; GOL: golimumab; TCZ: tocilizumab; TOFA: tofacitinib; RCT: randomized controlled trial; bDMARD: biologic DMARD; tsDMARD: targeted synthetic DMARD; pJIA: polyarticular JIA; sJIA: systemic JIA

good response to subsequent targeted therapies in several pJIA cohorts [2, 75, 141, 143, 146]. Finally, as for RA, switching to a non-TNF-inhibitor DMARD after TNF inhibitor failure does not seem more effective than switching to a second TNF inhibitor [2]. If these observations regarding the response to DMARDs are confirmed, the same questions arise: does pJIA represent a pathophysiological continuum (with varying severity) with additional factors determining the individual response to one or another DMARD, or are there distinct pJIA subtypes (based on synovial features) characterized by different inflammatory mechanisms (endotypes)? So far, few data are available to support one or the other hypothesis.

As for RA, heterogeneity in response to b/tsDMARDs in pJIA likely results from multiple factors, several of which are shared between the two conditions. Table 2 summarizes probable determinants of therapeutic response related to pJIA pathophysiology, individual patient characteristics, or drug-associated factors. Notably, evidence is relatively scarce for most of them, stressing the need for further research in the paediatric population.

For instance, synovial heterogeneity and its impact on therapeutic responses has been largely understudied in pJIA [23, 24]. Similarly, the notion of a window of opportunity in pJIA is widespread and has contributed to the implementation of treat-to-target strategies in pJIA, yet evidence supporting its existence is rather indirect [73]. Genetic studies investigating a possible link between specific SNPs and response to bDMARDs have been performed, but each have involved <100 JIA patients [76].

Drug plasma levels most likely play an important role in therapeutic efficacy in pJIA patients. This is illustrated by registry data showing that dose escalation is an effective option in JIA patients with an insufficient response to standard dosages of biologic therapy [147]. Of note, for a number of subcutaneously administered therapies, dosages are determined by weight or body surface categories rather than the individual patient weight [136, 143]. Currently, drug level measurements in blood are routinely available only for infliximab and adalimumab. While the association between blood levels of TNF inhibitors and clinical efficacy/flare prevention has been extensively studied in paediatric IBDs [148], this is not the

case for pJIA [149]. In contrast to paediatric Crohn's disease, therapeutic drug targets are unknown in pJIA [130]. Finally, insufficient drug levels can be a consequence of ADABs [149]. In JIA patients, a recent meta-analysis estimated the global prevalence of ADABs to be 16.9%, and possibly higher for certain bDMARDs [55]. Overall, while paediatric rheumatologists may monitor drug levels and ADABs, there is a paucity of evidence regarding how these results should modify their management.

Importantly, the observed overall similar efficacy of targeted b/tsDMARDs on articular disease in pJIA does not imply that second-line treatment can be randomly chosen for individual patients. Fig. 3 summarizes the predominant points to consider when selecting a specific DMARD on a personalized basis for pJIA patients. Presence of comorbidities, potential drug interactions, ways and frequency of administration, difficulties in treatment compliance, near-future pregnancy wishes, and/or cost are of particular relevance [100, 150–154]. Furthermore, evidence (or lack thereof) of long-term safety data is particularly critical in the guidance of therapy in children with chronic disease [155]. Specific national

reimbursement criteria will also frame therapeutic choices, although these may mostly be based on cost-related rationale.

### Predicting response to therapy in inflammatory arthritides

Better understanding of treatment response mechanisms could theoretically lead to the development of treatment-response prediction and thereby to numerous clinical advantages [77, 156]. The increasing number of available drugs, their cost, and the treat-to-target paradigm make this issue even more relevant for contemporary clinical practice. However, neither clinical data nor biomarker (nor combination thereof) have been confirmed to be of clinical use so far, given the relatively low predictive value of individual determinants of response. Nevertheless, interesting lessons have been learned. The most consistent finding in both RA and JIA is that patients with higher disease activity at baseline have a lower chance of achieving states of remission/low disease activity, regardless of the specific b/tsDMARD treatment [12, 14, 78, 79, 156–161]. By contrast, when considering relative/absolute improvement, higher baseline disease activity

	MTX	ADA	IFX	ETN	TCZ	ABA	GOL	TOFA	BAR	SEC
<b>COMORBIDITIES</b>										
UVEITIS			CP		CP					
PSORIASIS							?	?		?
AXIAL INVOLVEMENT				?			?	?		
IBD				?	?	?	? CU	? CU		?
ANA+ & YOUNG AGE										
LIPID DISTURBANCE										
HEPATIC INSUFFICIENCY										
RENAL INSUFFICIENCY										
RISK OR PRIOR TVE										
CYTOPENIA										
DRUG INTERACTIONS								CYP450 3A4	CYP450 3A4	
<b>OTHER FACTORS</b>										
ORAL ROUTE										
COMPLIANCE PROBLEM (or preferred i.v. route)					i.v.	i.v.	i.v.			
PREGNANCY WISHES										
MTX INTOLERANCE			?		?					
LONG-TERM SAFETY DATA <sup>†</sup>										

**Figure 3.** Personalized therapy for JIA in 2023. Selected factors and comorbidities guiding b/tsDMARD choice in clinical practice. Green indicates favourable choice, red indicates unfavourable choice, white indicates absence of good quality data. <sup>a</sup>We refer specifically to the existence of long-term safety data for children in large registries. Question mark: data suggested from adult studies, not yet confirmed in paediatric populations. CP: not supported by good quality evidence but largely used in clinical practice; CU: efficacy in colitis ulcerosa but not in Crohn's disease; ABA: abatacept; ADA: adalimumab; BAR, baricitinib; ETN: etanercept; GOL: golimumab; IFX: Infliximab; SEC: secukinumab; TCZ: tocilizumab; TOFA: tofacitinib; TVE: venous thromboembolism; bDMARD: biologic DMARD; tsDMARD: targeted synthetic DMARD



may be associated with greater measured change (the floor effect for low disease activity) [80, 162, 163]. Other factors associated with reduced therapeutic response include longer disease duration, and greater number of previously failed drugs (although data on the latter point lack good differentiation between primary and secondary non-response) [3, 4, 162]. The pattern of joint involvement was also found to influence response to therapies in JIA, with wrist/ankle involvement being associated with a more severe disease course [156, 164].

The link between seropositivity (for ACPA/RF) and disease outcomes has been studied in both RA and pJIA. Although seropositivity is consistently associated with a moderately increased risk of bone erosions and relapse after stopping the DMARD, its contribution to treatment response seems more complex [1, 156, 165, 166]. In RA, ACPA/RF presence has been initially linked with a moderate preferential response to abatacept and rituximab, but this signal was also seen for TNF inhibitors, suggesting that this association is not specific for therapies directly targeted against lymphoid cells [96, 129]. Therefore, neither EULAR nor ACR recommendations include seropositivity as an indication for selecting a specific bDMARD. RF titre could also potentially play a role through binding of the Fc $\gamma$  fraction of the bDMARDs, suggesting a beneficial role of Fc $\gamma$ -free drug, such as certolizumab-pegol in high-titre RF patients [167, 168].

Biomarkers studies have been performed in both RA and JIA. The results of the current literature have been reviewed recently [77, 96, 156, 169]. Perhaps not surprisingly, given the limited sample size, most results have not been replicated in further studies [129, 156]. Those studies were mostly based on retrospective data, but more recent work has taken a detailed look at potential precision medicine approaches. For instance, the R4RA trial investigated the link between the presence of synovial B cells and response to rituximab in an RCT setting, representing an important milestone in translational research. Notwithstanding its pathophysiological relevance, it yielded results of limited value from a clinical point of view [170].

Considering the multiple determinants of therapeutic response (see Table 2), only large datasets integrating multiple layers of data (genetic, clinical, pharmacological, immunological, etc.) are likely to capture the complexity of the response mechanisms and thus provide effective models for predicting therapeutic effect [163]. In conclusion, the field of biomarker studies is of utmost importance for better understanding of treatment–response mechanisms, and promising results are awaiting independent confirmatory studies. Nevertheless, current data on response prediction represent more stratification strategies than real ‘precision’ medicine, and they have limited added value for the clinical practice [171]. In addition, the direct clinical applicability of such expensive and time-consuming technologies could be limited. Therefore, personalized care (based on the individual patient’s comorbidities, drug–drug interactions, preferences, and personal situation) remains currently more relevant than biomarker-based stratified medicine [171, 172]. Of note, our review has mostly focused on the choice of targeted therapies; other relevant areas of personalized management (such as treatment tapering, prediction of drug side-effects, psychosocial interventions, etc.) have not been discussed here.

## Conclusion

The increasing understanding of key players in synovial inflammation has led to the development of effective targeted

therapies, yet their efficacy is highly variable among individuals with chronic arthritis. Individual determinants of response to therapies include several factors, related to disease pathophysiology (degree of core pathophysiological process activation, disease endotypes, or timing of therapy start), patient characteristics (genetic polymorphisms, comorbidities), environment or drug-specific factors (drug level, metabolism, etc.).

At the population level, ts/bDMARDs targeting different molecules display a similar efficacy in pJIA as in RA. Head-to-head comparative trials in JIA (with homogeneous patient populations) would be highly informative for refining therapeutic strategies. High-quality data are also needed in the field of therapeutic drug monitoring [70, 130], which has proven valuable in other inflammatory conditions.

Critical appraisal of the literature shows how the road towards reliable, reproducible and clinically applicable predictors of response to therapies remains long, since the complexity of treatment–response mechanisms is only beginning to be unravelled. Currently, personalized choice from among the available therapies should be based on consensus recommendations, taking into consideration comorbidities, drug safety profile, costs, and patient preferences.

In this review, we highlight a significant overlap in factors contributing to therapeutic response in RA and pJIA. This endorses the relevance of further collaboration between paediatrician and adult rheumatologists, patients, parents, and their representatives in the gaining of insights into response mechanisms to b/tsDMARDs, and fine-tuning personalized therapeutic approaches in children and adults with chronic inflammatory arthritis.

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