First-line biological versus conventional synthetic disease-modifying antirheumatic drug therapy in adult-onset Still's disease: a multicentre, retrospective, propensity weighted cohort study

Anna Kernder, Tim Filla, Rhea Friedrich, Norbert Blank, Diana Ernst, Jörg Henes, Gernot Keyßer, Philipp Klemm, Martin Krusche, Anna Meinecke, Jürgen Rech, Nils Schulz, Simon Michael Petzinna, Anne Pankow, Valentin S Schäfer, Alexander Pfeil, Sebastian Klapa, Eugen Feist, Stefan Vordenbäumen

Article - Version of Record

First-line biological versus conventional synthetic disease-modifying antirheumatic drug therapy in adult-onset Still's disease: a multicentre, retrospective, propensity weighted cohort study

Anna Kernder, Tim Filla, Rhea Friedrich, Norbert Blank, Diana Ernst, Jörg Henes, Gernot Keyßer, Philipp Klemm, Martin Krusche, Anna Meinecke, Jürgen Rech, Nils Schulz, Simon Michael Petzinna, Anne Pankow, Valentin S Schäfer, Alexander Pfeil, Sebastian Klapa, Eugen Feist, Stefan Vordenbäumen

Summary

Background Data on the efficacy of biological disease-modifying antirheumatic drug (DMARD) therapies such as anakinra, canakinumab, and tocilizumab as a primary therapeutic option in adult-onset Still's disease (AOSD) are scarce, and treatment recommendations rely mainly on data extrapolated from paediatric studies. The aim of this study was to compare the effectiveness of first-line biological DMARD therapy versus conventional synthetic DMARD therapy in AOSD.

Methods This multicentre, retrospective, propensity weighted cohort study was done at 16 secondary and tertiary rheumatology centres across Germany. Eligible patients were diagnosed with AOSD, met the Yamaguchi classification criteria, and had active disease without current treatment. All patients had documented follow-up assessments at weeks 12 and 72. The primary endpoint was sustained, event-free remission; a combined endpoint of sustained remission (C-reactive protein <10 mg/L and no arthritis, rash, or fever) and absence of complications during follow up in patients treated with first-line biological DMARDs (with or without glucocorticoids) or conventional synthetic DMARDs (methotrexate or glucocorticoids). Analysis was by propensity score weighted logistic regression, thereby balancing for the initial Pouchot score, ferritin concentration, and age and sex differences between groups. Analysis was done in the per protocol population. People with lived experience were not involved in the study design. The study is registered with the ISRCTN registry, ISRCTN86135778.

Findings Between Jan 1, 2007, and Sep 30, 2022, we screened 228 patients for inclusion. 142 patients were excluded, and 86 patients with AOSD who had an incident diagnosis or a flare without any maintenance treatment including glucocorticoids were enrolled and included in our analysis. 50 (58%) of 86 patients were female, 36 (42%) were male, and 84 (98%) were White. The mean age at inclusion was 39·4 years (SD 15·4). 44 (51%) of 86 had received a first-line biological DMARD and 42 (49%) received a first-line conventional synthetic DMARD. Biological DMARD therapy was associated with a greater likelihood of reaching the primary endpoint of sustained, event-free remission (OR 7·20, 95% CI 2·50–36·64; p=0·0007). At week 72, the rate of sustained, event-free remission was 50% (95% CI 34–65%; n=21) in the first-line biological DMARD group and 12% (3–23%; n=5) in the first-line conventional synthetic group. Glucocorticoid-related complications were more often described in the first-line conventional synthetic DMARD group (new-onset arterial hypertension [n=2] and glucocorticoid-related skin diseases [n=3]) versus none in the first-line biological DMARD group). Three (7%) of 42 patients in the conventional synthetic DMARD group died (two from macrophage activation syndrome, one unknown cause) versus none in the first-line biological DMARD group.

Interpretation First-line biological DMARD therapy in patients with AOSD showed a statistically significant association with sustained, event-free remission and fewer complications. Our findings highlight the potential of biologics to improve patient outcomes compared with conventional treatment options in AOSD.

Funding None.

Introduction

Still's disease is a rare inflammatory disease featuring intermittent high fever, an evanescent rash and arthritis or arthralgia, which can be complicated by a broad spectrum of additional organ manifestations, potentially culminating in the life-threatening manifestation of macrophage activation syndrome (MAS).[1] This disease has traditionally been separated into two entities based

Lancet Rheumatol 2025; 7: e415–23

Published Online March 28, 2025 https://doi.org/10.1016/S2665-9913(25)00023-2

See Comment page e381

Rheumazentrum Ruhrgebiet, Ruhr University Bochum, Herne, Germany (A Kernder MD); **Clinic for Rheumatology and Hiller Research Unit, University Hospital Düsseldorf, Medical Faculty of Heinrich-Heine University, Düsseldorf, Germany** (A Kernder, T Filla MSc, Prof S Vordenbäumen MD); **Justus-Liebig-University Giessen, Germany** (R Friedrich MD); **Helios Clinic Vogelsang-Gommern, Germany** (R Friedrich, Prof E Feist MD); **Experimental Rheumatology, Otto von Guericke University Magdeburg, Germany** (R Friedrich, Prof E Feist); **Department of Haematology, Oncology and Rheumatology, Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany** (Prof N Blank MD); **Department of Rheumatology and Immunology, Hannover Medical School, Hannover, Germany** (Prof D Ernst MD, A Meinecke MD); **Department of Internal Medicine II, Haematology, Oncology, Clinical Immunology, and Rheumatology, University Hospital Tübingen, Tübingen, Germany** (Prof J Henes MD); **Clinic for Internal Medicine II, Department of Internal Medicine, University Hospital Halle (Saale), Martin Luther University Halle-Wittenberg, Halle, Germany** (Prof G Keyßer MD); **Department of Rheumatology, Clinical Immunology,**

Osteology and Physical Medicine, Campus Kerckhoff, Justus-Liebig University Giessen, Bad Nauheim, Germany (P Klemm MD, N Schulz MD); **University Hospital Eppendorf, Department Internal Medicine III, Division of Rheumatology and Inflammatory Systemic Autoimmune Diseases, Hamburg, Germany** (M Krusche MD); **Department of Internal Medicine 3 - Rheumatology and Immunology, Deutsches Zentrum Immuntherapie and Center for Rare Diseases Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany** (J Rech MD); **Department of Rheumatology and Clinical Immunology, Clinic of Internal Medicine III, University Hospital of Bonn, Bonn, Germany** (S M Petzinna MD, Prof V S Schäfer MD); **Department of Rheumatology and Clinical Immunology, Campus Charité Mitte, Berlin, Germany** (A Pankow MD); **Department of Internal Medicine III, Jena University Hospital-Friedrich Schiller University Jena, Jena, Germany** (Prof A Pfeil MD); **Department of Rheumatology and Clinical Immunology, University of Lübeck, Lübeck, Germany and Institute of Experimental Medicine, Christian-Albrecht University Kiel, Kiel, Germany** (S Klapa MD); **Department of Rheumatology, St Elisabeth-Hospital Meerbusch-Lank, Meerbusch, Germany** (Prof S Vordenbäumen)

Correspondence to:
Prof Stefan Vordenbäumen, Department of Rheumatology, St Elisabeth-Hospital Meerbusch-Lank, 40668 Meerbusch, Germany
stefan.vordenbaeumen@rrz-meerbusch.de

Research in context

Evidence before this study

We searched PubMed and the Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V. (German guideline database) website between Jan 1, 2022, and Jan 1, 2023 for articles published since database inception. Evidence-based publications in German and English were included. We considered case series and observational studies (retrospective or prospective) with at least three patients, cross-sectional studies with at least three patients, randomised studies (with and without control), and systematic reviews. Search terms included "Still disease", "Still's disease", "systemic juvenile idiopathic arthritis", "AOSD", "biological therapy", "disease modifying agents", "anakinra", "canakinumab", "tocilizumab", "ciclosporin", and "methotrexate". The 2023 EULAR–PReS guidelines for treatment of Still's disease recommend the use of biological disease-modifying antirheumatic drugs (DMARDs) as a first-line therapy in all age groups. However, clinical approval studies for these empirically effective drugs all failed to reach their primary endpoint in adults, and approval of medication and recommendations from the most recently published treatment guidelines rely heavily upon efficacy data in children. Therefore in this study we determined whether first-line biological DMARD therapy was associated with more favourable outcomes compared with first-line conventional synthetic DMARD therapy.

Added value of this study

These data show, with a considerable effect size, that the use of biological DMARDs as a first-line therapy in patients with adult-onset Still's disease (AOSD) is clearly advantageous over first-line conventional synthetic DMARD therapy. This strengthens the most recent treatment recommendations and will impact future guidelines on AOSD.

Implications of all the available evidence

We expect these findings to influence decision making in initial AOSD treatment. This study helps to close an important knowledge gap, and supports the therapeutic approach of first-line biological DMARD therapy in AOSD which has been recommended in the 2023 EULAR–PReS guidelines. Finally, this study could inform future randomised trial design by providing data for sample size calculation, and the use of a combined endpoint.

on its onset in children or adults; systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD), respectively. However, newer approaches suggest that these conditions represent a continuum of the same disease, and a unified name, such as Still's disease, is increasingly preferred by many experts.

Glucocorticoids were traditionally used as first-line therapies for AOSD, with conventional synthetic disease-modifying antirheumatic drugs (DMARDs) serving as steroid-sparing agents, particularly methotrexate or ciclosporin.[2] Conventional synthetic DMARDs exhibit a slow onset of action, while the use of glucocorticoids is often associated with serious side effects, including diabetes and osteoporosis. Nowadays, biological DMARDs (ie, the IL-1 receptor antagonist anakinra, the IL-1β neutralising antibody canakinumab, and the IL-6 receptor antibody tocilizumab) are increasingly used. In fact, anakinra and canakinumab are licensed for use in AOSD in some countries.[3] In the 2024 EULAR–PReS-guidelines,[4] the use of biological DMARDs as a first-line therapy is recommended, while the use of conventional synthetic DMARDs is discouraged. According to registry data, a substantial number of patients with AOSD are in remission with conventional synthetic DMARDs, particularly methotrexate.[2] Moreover, both the licensing of anakinra and canakinumab for Still's disease in adults and children and the current EULAR–PReS recommendation for the use of biological DMARDs as a first-line therapy rely heavily upon efficacy data in children. Clinical approval studies in adults all failed to reach their primary endpoint.[5–7] The extrapolation is being justified by scarce indirect evidence from cohort studies in support of the use of biological DMARDs in adults[2,8] and overlapping pathogenesis, genetic predispositions, and clinical manifestations in adults and children, giving rise to the notion of a disease continuum.[8–10] Consequently, guidelines that specifically focused on studies in adults did not find enough evidence to exclusively recommend the use of biological DMARDs over conventional synthetic DMARDs as a first-line therapy in all patients with AOSD irrespective of disease activity.[3]

Unfortunately, high quality evidence data is difficult to obtain in a rare disease such as AOSD. Moreover, after licensing of biological therapies, one clinical study in adults had to be terminated prematurely for ethical concerns because licensed canakinumab would have had to be withheld from patients in the placebo group.[7]

The use of retrospective patient cohorts to address the question of whether biological DMARDs as a first-line therapy is advantageous in adults is complicated by inherent biases. In particular, patients with more active disease are much more likely to have been treated aggressively from the outset and might also carry a higher risk of complications and flares during follow-up. Therefore, propensity score weighted analyses of retrospective data have been advocated to yield more reliable information, since important selection biases such as disease activity at onset can be accounted for.[11] We registered a study with fixed endpoints, collected patient data in multiple centres, and did a weighted analysis under the hypothesis that first-line therapy with biological DMARDs leads to a higher rate of sustained remission with less complications during follow-up than conventional synthetic DMARDs.

Methods

Study design and participants

In this multicentre, retrospective cohort study, patients with AOSD from 16 secondary and tertiary rheumatology centres in Germany were included (appendix p 3) between Jan 1, 2007, and Sept 30, 2022. Patients were eligible for inclusion if they fulfilled the Yamaguchi criteria[12] with the exception that inactive malignancy, rheumatic disease, or minor infection was not considered to be an exclusion criterion if determined to be unrelated to ASOD by the treating physician or were treated with first-line therapy with any of the substances included in the German guidelines[3] (ie, prednisolone, methotrexate, and ciclosporine [conventional synthetic DMARDs] or anakinra, canakinumab, and tocilizumab [biological DMARDs]). Patients were eligible for inclusion if they had incident diagnoses or a flare without any maintenance treatment including glucocorticoids. Glucocorticoids were allowed in both treatment groups.

Exclusion criteria included treatment with first-line therapy with etoposide or experimental substances, pregnancy during follow-up, and documented non-compliance. Patients in remission at week 0 were also excluded (defined as absence of all of C-reactive protein [CRP] >10 mg/L, fever, arthritis, and rash during the last week).

Options for data on sex were male, female, or diverse. Ethnicity was categorised as White, Black, Asian, South American, mixed, and missing. Sex and ethnicity were reported by clinicians from patients' medical records.

This study was approved by the Heinrich-Heine-University Duesseldorf Institutional Review Board (2023-2423_1) and was registered with the ISRCTN registry (www.isrctn.com) before data collection (ISRCTN86135778). The ethics committee deemed the study exempt from requiring informed consent. People with lived experience were involved in the German guidelines process leading up to the research question adressed, but were not involved in the design of the study.

Procedures

Medical charts were retrospectively reviewed by a rheumatologist at the respective site between May 1, 2023, and Aug 31, 2024, to collect demographic, clinical, laboratory, treatment, and outcome data at the beginning of diagnosis or time of a flare of the disease (week 0), at week 12 (accepted range 6–24) and week 72 (accepted range 60–100). Events that occurred in between the assessments were attributed to the next timepoint. All patients had documented follow-up assessments at week 12 (6–24) and 72 (60–100). All data were collected using a standardised case report form, developed at the coordinating centre (Heinrich-Heine University, Düsseldorf, and St Elisabeth-Hospital, Meerbusch-Lank) and shared with all participating centres. Adherence to case-finding regulations (inclusion and exclusion criteria) and follow-up assessments at week 12 (range 6–24) and 72 (60–100) was verified at entry by two independent rheumatologists (AK and SV) and ineligible cases were excluded. Centres were asked to document every patient with AOSD fulfilling the inclusion criteria or not fulfilling the exclusion criteria between Jan 1, 2007, and Sept 30, 2022 to minimise potential selection bias.

See Online for appendix

Outcomes

The primary outcome was sustained, event-free remission; a combined endpoint of sustained remission and an event-free state at week 12 and week 72. Sustained remission was defined as CRP lower than 10 mg/L and the absence of fever, arthritis, and AOSD-associated rash beginning at week 12 and maintained throughout week 72. An event-free state was defined as no complication from week 12 to week 72 from medication use or AOSD flare including complication of glucocorticoid use (in the context of this study, an event was defined as any type of diabetes necessitating insulin therapy, osteonecrosis of any joint, psychosis or other psychiatric disease requiring psychopharmacological intervention, hypertension resulting in change of antihypertensive medication, dyslipidaemia requiring therapy, clinical diagnosis of steroid myopathy, skin disease attributed to glucocorticoid use, eye disease attributable to glucocorticoid use [especially cataract or glaucoma, as determined by the treating rheumatologist]), serious infection necessitating intravenous antibiotic use, AOSD-associated pneumonitis, ASOD-associated perimyocarditis, death or development of MAS, or the need for therapy escalation (change from a conventional synthetic DMARD to biological DMARD). As there are no consensus diagnostic criteria for AOSD-MAS, the diagnosis was made by the centres with respect to current recommendations[13] and plausibility checked upon data entry (AK and SV).

Secondary outcomes included the above endpoints not combined, discontinuation of glucocorticoids and absolute reduction, the primary endpoint with switching of medication to a biological DMARD not regarded as an event. Subgroup analyses of the primary endpoint for patients having received first-line IL-1 or IL-6-targeted therapy was also done. We decided not to calculate the following secondary endpoints due to unprecise primary data or missing data: retrospective analysis of differences in the glucocorticoid toxicity index, time to remission, time to complication, and flare-free survival in patients under remission.

Multiple post-hoc sensitivity analyses were done for the primary endpoint, which included; disregarding medication switch as an event (ie, enabling patients to switch from a conventional synthetic DMARD to biological DMARD without denoting treatment failure), omitting ferritin as a confounder, performing a complete case analysis (ie, excluding patients with missing data),

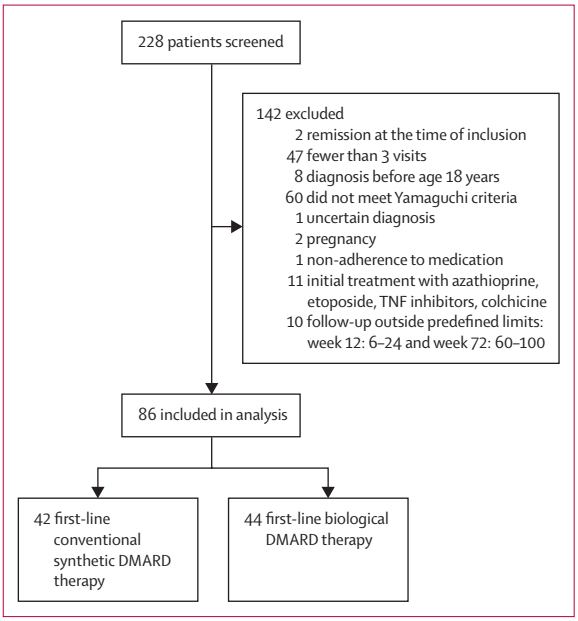

Figure 1: **Trial profile**

additionally excluding a patient who was on immunoglobulin replacement therapy at the time of inclusion, additionally adjusting for initial CRP concentration, neutrophil count, and aspartate aminotransferase concentration.

Statistical analysis

The analysis group consisted of patients with AOSD on a biological or conventional synthetic DMARD therapy. Data are presented as mean (SD) in case of normal distribution, median (IQR) for continuous variables, and as absolute n (%) for qualitative variables. To account for selection bias for first-line biological versus conventional synthetic DMARD therapy, we applied propensity score weighting using overlap weights.[14] The propensity scores were estimated by logistic regression with potential confounders; initial disease activity measured by the Pouchot score (numerical value from 0 [no disease activity] to 12 [high disease activity]),[15] ferritin concentration (mg/dL), age (years), and sex as the independent variables. The set of confounders was defined by expert consensus. Balance was evaluated by comparison of confounders after weighting in both groups. Subsequently, weighted linear regression (continuous outcome) or weighted logistic regression modelling (binary outcome) was done with therapy group (first-line biological or conventional synthetic DMARD therapy) as the dependent variable and the respective outcomes as the independent variable. 95% CIs were calculated using the 2·5th and 97·5th percentiles of the bootstrap distribution based on 10 000 iterations, whereby in each iteration both the weight estimation and effect estimation step were repeated. p values were derived by permutation testing with 10 000 iterations. Thus, CIs and p values might be slightly discrepant. If a clinical event or complication was found in chart review, the event was designated as present, otherwise the value was set to 0. Median

	First-line conventional synthetic DMARD therapy (n=42)	First-line biological DMARD therapy (n=44)
Age at inclusion (years)	41·4 (14·6)	37·5 (16·0)
Sex		
Male	18 (43%)	18 (41%)
Female	24 (57%)	26 (59%)
Ethnicity		
White	40 (95%)	44 (100%)
Mixed	1 (2%)	0
South American	1 (2%)	0
Symptoms		
Fever*	42 (100%)	41 (93%)
Arthralgia	35 (83%)	40 (91%)
Arthritis	19 (45%)	17 (39%)
Hepatomegaly or splenomegaly	34 (81%)	37 (87%)
Rash	31 (74%)	37 (84%)
Leukocytosis†	31 (74%)	35 (80%)
Pharyngodynia	23 (55%)	30 (68%)
Lymphadenopathy	19 (45%)	21 (48%)
Pouchot score‡	5·0 (5·0–6·0)	5·0 (4·0–7·0)
Symptom duration (months)	2 (0·5–4·0)	1 (1·0–4·0)
Laboratory parameters		
Serum ferritin concentration (µg/L)§	2890 (1004–7280)	2255 (1247–10510)
CRP (mg/L)	118 (70–205)	146 (86–208)
CRP >10 mg/L¶	38 (90%)	43 (98%)
Aspartate aminotransferase (mg/dL)	59·0 (37·5–71·5)	59·0 (37·4–74·2)
Alanine aminotransferase (mg/dL)	51·0 (43·3–114·5)	51·0 (35·8–76·8)
Neutrophils (cells per nL)	12·0 (12·0–13·4)	12·0 (9·1–14·3)
Medication		
Glucocorticoids	42 (100%)	34 (77%)
Glucocorticoid dose (mg per day)	55·0 (40·0–78·8)	55·0 (4·0–100·0)
Methotrexate	12 (29%)	8 (18%)
Anakinra	0	37 (84%)
Canakinumab	0	2 (5%)
Tocilizumab	0	5 (11%)
Immunoglobulins	1 (2%)	0

Data are n (%), mean (SD), or median (IQR). AOSD=adult-onset Still's disease. CRP=C-reactive protein. DMARD=disease-modifying antirheumatic drug. *Fever greater than 39°C for at least 1 week. †Leukocytosis over 10 000/µL with more than 80% neutrophils. ‡Pouchot Score is a sum of AOSD manifestations ranging from 0 (no disease activity) to 12 (high disease activity). §Normal range 20–250 µg/L, markedly raised concentrations indicate active AOSD. ¶Normal range less than 5 mg/L, mild elevation 5–10 mg/L, moderate to marked elevation greater than 10 mg/L.

Table 1: **Baseline characteristics**

imputation was used for missing values of CRP and ferritin concentration. Data were analysed with R (version 4.1.2).

Role of the funding source

There was no funding source for this study.

Results

Between Jan 1, 2007, and Sep 30, 2022, we screened 228 patients across 16 secondary and tertiary rheumatology centres in Germany for inclusion in this study. 142 patients were excluded, and 86 were included in this analysis (figure 1). 50 (58%) of 86 patients were female, 36 (42%) were male, and 84 (98%) were White. The mean age at inclusion was 39·4 years (SD 15·4; table 1). The median duration of symptoms before diagnosis was 2 months (IQR 1–4). The most frequent clinical manifestations at diagnosis included fever (83 [97%] of 86 patients), arthralgia (75 [87%]) and rash (68 [79%]). Median CRP at diagnosis was 139·2 mg/L (IQR 76·8–206·8) and median ferritin concentration was 2890·0 µg/L (IQR 1183·3–9191·0; table 1). Median imputation was used for missing values of CRP (one patient at week 0, 13 patients at week 12, and ten patients at week 72) and ferritin (six patients at week 0). There was no incident case of AOSD lung disease.

42 (49%) of 86 patients received first-line conventional synthetic DMARD therapy; 12 (29%) of 42 received methotrexate (with glucocorticoids), 30 (71%) received glucocorticoid monotherapy and one (2%) received immunoglobulin therapy. 44 (51%) of 86 patients received first-line biological DMARD therapy; 37 (84%) of 44 received anakinra (nine [24%] of whom later switched to canakinumab due to injection site reactions), two (5%) received canakinumab and five (11%) received tocilizumab (table 1). Ten (23%) had no glucocorticoid therapy. The median glucocorticoid dosage at week 0 was 55·0 mg per day (IQR 32·5–80·0) in both groups (table 1).

Weighting was performed for differences in important confounders (table 2). For example, mean serum ferritin concentration was higher in the group of patients receiving initial biological DMARD therapy (12496·6 µg/L [SD 25797·1]) compared with the initial conventional synthetic DMARD therapy group (6985·4 µg/L [9737·4]; table 2). Data on specific events and remission in the unweighted cohort are reported in the appendix (p 2).

Weighted regression models were applied, with therapy type (first-line biological or conventional synthetic DMARDs) as the independent variable and respective outcomes as dependent variables, as indicated. After overlap weighting, the effective sample size was 41·2 in the conventional synthetic DMARD group and 42·2 in the biological treatment group. For ease of interpretation, we report the rounded numbers.[16]

First-line biological DMARD therapy was associated with substantially higher chances of reaching the primary endpoint of sustained, event-free remission (odds ratio [OR] 7·20, 95% CI 2·50–36·64; p<0·0007; figure 2). The proportion of patients in sustained, event-free remission on first-line biological DMARD therapy was higher than that in patients on first-line conventional synthetic DMARD therapy at week 12 (27 [64%] of 42 patients on biological DMARD therapy [95% CI 49–79%] *vs* 13 [32%] of 41 patients on conventional synthetic DMARD therapy [18–47%]) and week 72 (21 [50%] of 42 patients on biological DMARD therapy [34–65%] *vs* five [12%] of 41 patients on conventional synthetic DMARD therapy [3–23%]; figure 3).

We did subgroup analyses for patients on a first-line IL-1 inhibitor strategy who switched to an IL-6 inhibitor due to inadequate treatment response, and vice versa. Patients on first-line IL-1 inhibitors had a higher probability of reaching the primary endpoint of sustained, event-free remission compared with conventional synthetic DMARD therapy (OR 7·49 95% CI 2·68–39·16; p=0·0003; figure 2). There was no statistically significant association of a first-line IL-6 inhibitor treatment with reaching the primary endpoint (2·15, $9·1\times10^{-9}$–2698·6; p=0·5).

Five patients received tocilizumab as first-line therapy. Of these five patients, one (20%) fulfilled the primary endpoint of sustained, event-free remission, while the others developed fever (two [40%]), rash (one [20%]), and arthritis (one [20%]) during follow-up, and three (60%) discontinued glucocorticoids by week 72. None of the patients died. Three patients (60%) remained on tocilizumab until week 72, one switched to canakinumab, and one patient discontinued in remission.

	Overall (n=86)	First-line conventional synthetic DMARD therapy (n=42)	First-line biological DMARD therapy (n=44)	First-line conventional synthetic DMARD therapy weighted (n=41)	First-line biological DMARD therapy weighted (n=42)
Pouchot Score*	5·5 (1·7)	5·4 (1·3)	5·6 (2·0)	5·4 (1·3)	5·4 (1·9)
Male Sex	36 (42%)	18 (43%)	18 (41%)	17 (41%)	18 (43%)
Age at diagnosis (years)	39·4 (15·4)	41·4 (14·6)	37·6 (16·0)	39·9 (14·0)	39·9 (16·4)
Ferritin concentration (µg/L)	9804·6 (19750·2)	6985·4 (9737·4)	12495·6 (25797·1)	7619·8 (10363·1)	7619·8 (14448·9)

Data are n (%) or mean (SD). DMARD=disease-modifying antirheumatic drug. *Pouchot Score is a sum of AOSD manifestations ranging from 0 (no disease activity) to 12 (high disease activity).

Table 2: **Unweighted and weighted confounders**

	First-line conventional synthetic DMARD therapy			First-line biological DMARD therapy			Odds ratio (95%CI)
	Number of events/ number at risk	%	% weighted	Number of events/ number at risk	%	% weighted	
Primary analysis							
Sustained, event-free remission	5/42	11·9	12·1	21/44	47·7	49·7	7·20 (2·50–36·64)
Additional analyses of key secondary endpoints							
Sustained, event-free remission (medication switch disregarded)	11/42	26·2	26·2	21/44	47·7	47·7	2·57 (1·03–7·39)
Sustained, event-free remission (IL-1 inhibitor only)	15/42	35·7	35·9	23/40	57·5	58·0	7·49 (2·68–39·16)
Event-free	18/42	42·9	43·0	37/44	84·1	83·9	6·89 (2·66–24·90)
Event-free (medication switch disregarded)*	32/42	76·2	77·1	37/44	84·1	83·9	1·54 (0·52–5·58)
Sustained remission	15/42	35·7	37·0	24/44	54·5	56·2	2·18 (0·92–5·64)
Stop glucocorticoids at week 12	7/42	16·7	15·8	14/44	31·8	33·9	2·74 (1·04–9·10)
Stop glucocorticoids at week 72	18/42	42·9	42·7	32/44	72·2	72·5	3·54 (1·43–10·08)

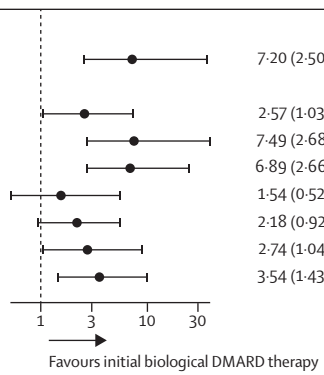

Figure 2: **Odds ratios for the primary and key secondary endpoints**
Odds ratios calculated by weighted binary logistic regression analysis comparing first-line biological DMARD therapy to first-line conventional synthetic DMARD therapy in patients with adult-onset Still's disease. DMARD=disease-modifying antirheumatic drug. *A switch from conventional synthetic DMARD therapy to a biological DMARD therapy was not counted as an event in this analysis.

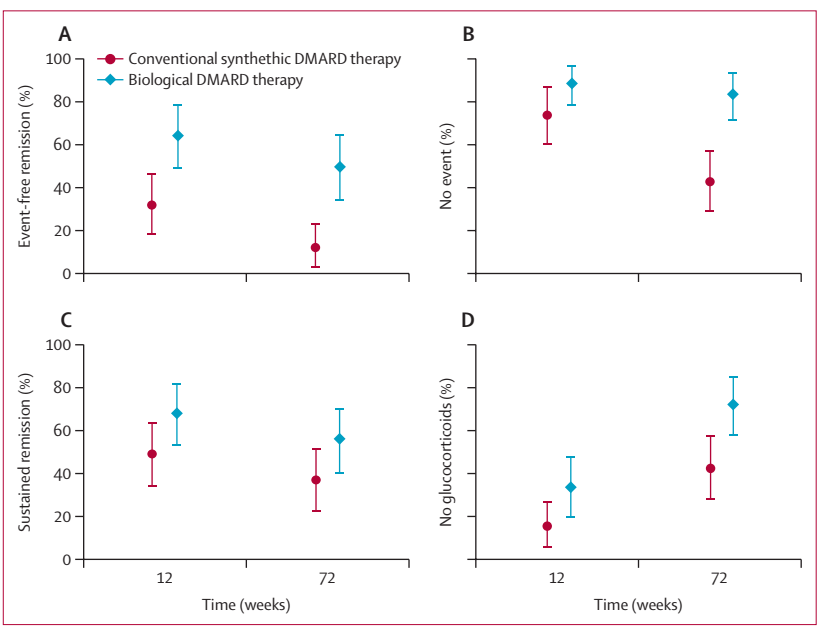

Figure 3: **Proportion of patients reaching the primary and key secondary endpoints**
Proportion (%) of patients reaching (A) event-free remission, (B) no event, (C) sustained remission and (D) no glucocorticoid use at weeks 12 and 72. Error bars indicates 95% CIs calculated by bootstrapping. DMARD=disease-modifying antirheumatic drug.

When analysing the single components of the combined endpoint, first-line biological DMARD therapy was associated with a greater chance of maintaining an event-free state (OR 6·89, 95% CI 2·66–24·90; p<0·0001; figure 2). The proportion of patients on first-line biological DMARD therapy versus conventional synthetic DMARD therapy without an event was higher at week 12 (38 [90%] of 42 patients on biological DMARD therapy [78–97%] *vs* 30 (73%) of 41 patients on conventional synthetic DMARD therapy [60–87%]) and week 72 (35 [83%] of 42 patients on biological DMARD therapy [72–94%] *vs* 18 [44%] of 41 patients on conventional synthetic DMARD therapy [29–58%]; figure 3). Patients on a conventional synthetic DMARD experienced 0·79 events [95% CI 0·5–1·0]. This was reduced in patients receiving first-line biological DMARD therapy by 0·57 events [0·55–0·93] to 0·22 events (p=0·002 according to weighted regression modelling). In terms of absolute numbers, the most common complications were the necessity to switch medication due to treatment failure (19 [22%] of 86 patients) and infections (ten [12%]). Two (5%) of 42 patients in the first-line conventional synthetic DMARD group developed MAS (one at week 12 and one at week 72) which was attributed to AOSD without any additional factor such as infection or malignancy identified, and both died due to MAS-associated multi-organ failure. One (2%) of 42 patients in the conventional synthetic DMARD group died of unknown causes without evidence of MAS at the time of death. All deaths outlined occurred at week 72. No patient in the first-line biological DMARD group developed MAS or died during follow-up. In case a change of medication was not regarded as an event, the effect was considerably smaller and no longer statistically significant (OR 1·54, 95% CI 0·52–5·58; p=0·26; figure 2).

First-line biological DMARD therapy was associated with a greater chance of maintaining sustained remission (OR 2·18, 95% CI 0·92–5·64; p=0·047 by permutation testing; figure 2). The proportion of patients in sustained remission with a first-line biological DMARD versus a conventional synthetic DMARD therapy was higher at week 12 (29 [69%] of 42 patients on biological DMARD

therapy [95% CI 53–82%] *vs* 20 [49%] of 41 patients on conventional synthetic DMARD therapy [34–64%]) and week 72 (24 [57%] of 42 patients on biological DMARD therapy [40–71%] *vs* 15 [37%] of 41 patients on conventional synthetic DMARD therapy [22–52%]; figure 3).

Glucocorticoid-related complications were described more often in the first-line conventional synthetic DMARD group, for example, new-onset arterial hypertension (n=2) and glucocorticoid-related skin diseases (n=3; *vs* none of either in the biological DMARD group). Likelihood of discontinuing glucocorticoids was higher in the first-line biological DMARD group at week 12 (OR 2·74, 95% CI 1·04–9·10; p=0·027) and at week 72 (3·54, 1·43–10·08; p=0·0045; figure 2). The proportion of patients without glucocorticoids in the first-line biological DMARD group versus the conventional synthetic DMARD group was higher at week 12 (14 [33%] of 42 patients [20–48%] *vs* seven [17%] of 41 patients [6–28%]) and week 72 (31 [74%] of 42 patients [58–86%] *vs* 18 [44%] of 41 patients [28–58%]; figure 3). Patients on first-line biological DMARD therapy reduced the average daily dose of glucocorticoids compared with those on conventional synthetic DMARD therapy by 60·2 mg versus 30·6 mg at week 12 (p=0·073), and by 67·8 mg versus 61·9 mg at week 72 (p=0·36).

The results of the sensitivity analyses was robust in comparison to the original primary outcome in all of the following scenarios: disregarding medication switch as an event (ie, enabling patients to switch from conventional to biological DMARD therapy without denoting treatment failure [OR 2·57, 95% CI 1·03–7·39; p=0·023, figure 2]), omitting ferritin as a confounder (6·87, 2·44–36·02; p=0·0007), performing a complete case analysis (ie, excluding patients with missing data [8·01, 2·43–45·58; p=0·0005), excluding a patient who was on immunoglobulin replacement therapy at the time of inclusion (7·66, 2·33–42·41; p=0·0003), adjusting for initial CRP concentration, neutrophil count, and aspartate aminotransferase concentration (6·58, 2·22–34·57; p=0·0007).

Discussion

In this study we show that first-line biological DMARD therapy is associated with advantageous outcomes in patients with AOSD when compared with first-line conventional synthetic DMARD therapy. In particular, the primary endpoint of sustained, event-free remission was reached at a considerable effect size and was robust in multiple sensitivity analyses. This finding is further supported by those receiving first-line biological DMARD therapy reaching key secondary endpoints of reduction of glucocorticoids and complications.

We selected a combined primary endpoint. Sustained remission alone, while important, does not capture the full spectrum of patient and physician goals, which also include avoiding side effects and the need to switch therapies.

Previous studies in AOSD were unable to demonstrate statistically significant effects of first-line biological DMARD therapies compared with conventional synthetic DMARD therapies. We assume several reasons for this. First, our endpoint differs from the limited randomised controlled trials in AOSD for anakinra (remission, ie, no fever, arthritis, raised CRP or ferritin concentration, or intake of non-steroidal anti-inflammatory drugs at week 8 and 24),[6] canakinumab (reduction of rheumatoid arthritis disease activity score 28 at week 12)[17] and tocilizumab (American College of Rheumatology 50 response at week 4).[5] Second, by extending the observational period, we were able to capture glucocorticoid side effects and complications which might have gone unnoticed in these trials. Third, the number of participants in these prospective studies was very small (19–27 participants). Fourth, by contrast with the randomised controlled trials, our study was retrospective in nature, however, case weighting was employed to adjust for important confounders.[11] In this regard, our study extends on the knowledge gained from existing meta-analyses and systematic reviews that showed favourable response and remission rates of anakinra, canakinumab[18–22] and tocilizumab.[22,23]

In line with the observations in this study, response rates to biological DMARD therapies of around 70–80% have been reported in both adults[24] and children.[25,26] Thus, this study further supports the notion of similar disease responses and supposed pathophysiology in adult and paediatric onset Still's disease.

This study has several limitations. The effects we observed must be interpreted as associations, as causation cannot be determined. Retrospective studies carry the inherent potential for bias such as selection bias and rely on existing medical records. To compensate for these factors, we applied strict quality control of the data that rendered around 60% of reported cases ineligible. Moreover, weighting was used to control for important measures of disease activity which might have influenced initial treatment decisions and confer different chances of complications during follow-up. Importantly, study design and endpoints were defined and registered before the initiation of data collection. Patients on a first-line treatment with an IL-1 inhibitor were over-represented. This limits generalisability. The number of patients on first-line IL-6 inhibition was small; as such, there was no statistically significant association for the primary outcome and CIs were wide. We do not believe that superiority of first-line IL-1 inhibition over IL-6 inhibition can be derived from our data.

In addition, we could not unequivocally allocate patients to either a chronic articular or a systemic disease subtype from the retrospective data, and hence did not account for these phenotypes. Although recent analyses challenge the traditional concept of these phenotypes[10] and no striking difference has been noted in treatment responses in either entity,[8,27,28] we cannot completely

exclude the risk of having introduced a bias. Furthermore, events were reported as absent or present. In many cases, no precise date could be recorded. This would have enabled us to compare if the time to an event or remission was different. Our combined endpoint includes the occurrence of events which might seem acceptable such as new onset arterial hypertension. Only two (2%) of 86 patients were diagnosed with MAS, when the rate of patients with MAS would be expected to be around 10% in Still's disease across all ages.[29] However, rates as low as 1·5% have been reported in adults.[30]

Some patients were followed throughout the COVID-19 pandemic. Even though we did not find any indication that a recorded event or flare was attributable to SARS-CoV-2 infection, and consequent screening procedures were obligatory in German clinics at the time, we cannot completely rule out that this could have influenced the disease course in some patients. Finally, the number of patients analysed, even though larger than in previous clinical trials, is still small. This small patient number explains the fairly wide CIs.

So far, the efficacy of first-line biological DMARD therapy versus conventional synthetic DMARD therapy for AOSD has largely been extrapolated from studies in children. Here, we provide evidence for more advantageous health benefits for first-line biological DMARD therapy versus conventional synthetic DMARD therapy in AOSD. This study helps to close an important knowledge gap and supports the therapeutic approach of first-line biological DMARD therapy in this population. Finally, this study could help to inform future randomised trial design by providing data for sample size calculation, and the use of a combined endpoint.

Contributors

AK contributed to the literature search, study design, data collection, data interpretation, and writing of the original draft. TF contributed to the data interpretation, data analysis, writing review, and editing. RF contributed to the data collection, writing review, and editing. NB, DE, JH, GK, PK, MK, AM, JR, NS, SMP, VSS, APf, APa and SK contributed to the data collection, writing review, and editing. EF contributed to the conceptualisation, data collection, supervision, validation, writing review, and editing. SV contributed to the conceptualisation, supervision, literature search, study design, data analysis, visualisation, data interpretation, validation, and writing original draft. AK, TF, RF and SV accessed and verified the data underlying the study. All authors had full access to all data in the study, reviewed and approved the final manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

SV received a speaking fee from SOBI. RF received a scholarship (Maja-Völkel-Promotionsstipendium) from the German society for Rheumatology and Clinical Immunology. EF received grants from Lilly, Galapagos, Novartis, speaking fees from AbbVie, Bristol Myers Squibb, Lilly, Pfizer, SOBI, Novartis, and Roche/Chugai; support for travel from Novartis; and fees for participation on advisory boards from AbbVie Lilly, Novartis. DE received speaking fee from Roche/Chugai. JR received grants from SOBI, Novartis, consulting fees from AbbVie, Celgene, Janssen, Novartis, SOBI, and UCB; speaking fees from AbbVie, Bristol Myers Squibb, Janssen, Novartis, SOBI, and UCB; travel support from UCB; and participated on advisory boards for SOBI and Novartis. SK received a speaking fee from Novartis. NB received speaking fees from SOBI, Novartis, and Boehringer Ingelheim and support for travel from SOBI, Roche, and Novartis. JH received unrestricted grants from SOBI and Novartis and honoraria for speakers' bureaus from AstraZeneca, Bristol Myers Squibb, GSK, Boehringer Ingelheim, UCB, SOBI, and Roche. MK received research support from SOBI and Sanofi; consulting fees from SOBI, Novartis, and AlphaSigma; speaking fees from SOBI, Novartis, AbbVie, UCB, Lilly, AlphaSigma, Bristol Myers Squibb, Pfizer, FOMF Akademie, and Deutsche Rheumaakademie; and travel support from AbbVie. All other authors declare no competing interests.

Data sharing

Deidentified participant data will be made available upon reasonable request to the corresponding author, after approval of a proposal, with a signed data access agreement.

References

1 Efthimiou P, Kadavath S, Mehta B. Life-threatening complications of adult-onset Still's disease. *Clin Rheumatol* 2014; **33:** 305–14.

2 Ruscitti P, Masedu F, Vitale A, et al. The systemic score may identify life-threatening evolution in still disease: data from the GIRRCS AOSD-study group and the AIDA network still disease registry. *Arthritis Rheumatol* 2024; **76:** 1141–52.

3 Vordenbäumen S, Feist E, Rech J, et al. [DGRh S2e guidelines: diagnostic and treatment of adult-onset Still's disease (AOSD)]. *Z Rheumatol* 2022; **81** (suppl 1)**:** 1–20.

4 Fautrel B, Mitrovic S, De Matteis A, et al. EULAR/PReS recommendations for the diagnosis and management of Still's disease, comprising systemic juvenile idiopathic arthritis and adult-onset Still's disease. *Ann Rheum Dis* 2024; **83:** 1614–27.

5 Kaneko Y, Kameda H, Ikeda K, et al. Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. *Ann Rheum Dis* 2018; **77:** 1720–29.

6 Nordström D, Knight A, Luukkainen R, et al. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. *J Rheumatol* 2012; **39:** 2008–11.

7 Kedor C, Listing J, Zernicke J, et al. Canakinumab for treatment of adult-onset Still's disease to achieve reduction of arthritic manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Ann Rheum Dis* 2020; **79:** 1090–97.

8 Vitale A, Caggiano V, Lopalco G, et al. Still's disease continuum from childhood to elderly: data from the international AIDA Network Still's disease registry. *RMD Open* 2023; **9:** e003578.

9 Ruscitti P, Natoli V, Consolaro A, et al. Disparities in the prevalence of clinical features between systemic juvenile idiopathic arthritis and adult-onset Still's disease. *Rheumatology (Oxford)* 2022; **61:** 4124–29.

10 Ruscitti P, Masedu F, Vitale A, et al. Derivation and validation of four patient clusters in Still's disease, results from GIRRCS AOSD-study group and AIDA Network Still Disease Registry. *RMD Open* 2023; **9:** e003419.

11 Almaghlouth I, Pullenayegum E, Gladman DD, Urowitz MB, Johnson SR. Propensity score methods in rare disease: a demonstration using observational data in systemic lupus erythematosus. *J Rheumatol* 2021; **48:** 321–25.

12 Yamaguchi M, Ohta A, Tsunematsu T, et al. Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; **19:** 424–30.

13 Shakoory B, Geerlinks A, Wilejto M, et al. The 2022 EULAR/ACR points to consider at the early stages of diagnosis and management of suspected haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). *Arthritis Rheumatol* 2023; **75:** 1714–32.

14 Li F, Morgan KL, Zaslavsky AM. Balancing Covariates via Propensity Score Weighting. *J Am Stat Assoc* 2018; **113:** 390–400.

15 Pouchot J, Sampalis JS, Beaudet F, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine (Baltimore)* 1991; **70:** 118–36.

16 Hanberg JS, Fu X, Wang X, et al. Effectiveness of a fourth dose of COVID-19 mRNA vaccine in patients with systemic autoimmune rheumatic diseases using disease-modifying antirheumatic drugs: an emulated target trial. *Lancet Rheumatol* 2024; **6:** e21–30.

17 Kedor C, Listing J, Zernicke J, et al. Canakinumab for treatment of adult-onset Still's disease to achieve reduction of arthritic manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Ann Rheum Dis* 2020; **79:** 1090–97.

18 Fautrel B, Patterson J, Bowe C, et al. Systematic review on the use of biologics in adult-onset still's disease. *Semin Arthritis Rheum* 2023; **58:** 152139.

19 Giacomelli R, Sota J, Ruscitti P, et al. The treatment of adult-onset Still's disease with anakinra, a recombinant human IL-1 receptor antagonist: a systematic review of literature. *Clin Exp Rheumatol* 2021; **39:** 187–95.

20 Cota-Arce JM, Cota J, De León-Nava MA, et al. Efficacy and safety of canakinumab in the treatment of adult-onset Still's disease: a systematic review. *Semin Arthritis Rheum* 2021; **51:** 1282–90.

21 Feist E, Quartier P, Fautrel B, et al. Efficacy and safety of canakinumab in patients with Still's disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups. *Clin Exp Rheumatol* 2018; **36:** 668–75.

22 Ruscitti P, McGonagle D, Garcia VC, et al. Systematic review and meta-analysis of pharmacological interventions in adult-onset Still's disease highlights the beneficial role of biologic DMARDs. *J Rheumatol* 2024; https://www.jrheum.org/content/early/2024/01/25/jrheum.2023-0995 (accessed Nov 8, 2024).

23 Ma Y, Wu M, Zhang X, et al. Efficacy and safety of tocilizumab with inhibition of interleukin-6 in adult-onset Still's disease: a meta-analysis. *Mod Rheumatol* 2018; **28:** 849–57.

24 Ruscitti P, Ursini F, Cipriani P, De Sarro G, Giacomelli R. Biologic drugs in adult onset Still's disease: a systematic review and meta-analysis of observational studies. *Expert Rev Clin Immunol* **13:** 1089–97.

25 Nigrovic PA, Mannion M, Prince FHM, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. *Arthritis Rheum* 2011; **63:** 545–55.

26 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:** 1163–73.

27 Sota J, Vitale A, Lopalco G, et al. Efficacy and safety of tocilizumab in adult-onset Still's disease: real-life experience from the international AIDA registry. *Semin Arthritis Rheum* 2022; **57:** 152089.

28 Vitale A, Caggiano V, Maggio MC, et al. Canakinumab as first-line biological therapy in Still's disease and differences between the systemic and the chronic-articular courses: real-life experience from the international AIDA registry. *Front Med (Lausanne)* 2022; **9:** 1071732.

29 Neau PA, El-Jammal T, Javaux C, et al. The spectrum of Still's disease: a comparative analysis of phenotypic forms in a cohort of 238 patients. *J Clin Med* 2022; **11:** 6703.

30 Adachi S, Takase-Minegishi K, Maeda A, et al. Risk of macrophage activation syndrome in patients with adult-onset still's disease treated with IL-1 and IL-6 inhibitors: a meta-analysis and single-center experience. *Rheumatol Ther* 2023; **10:** 1623–36.