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REVIEW

Efficacy and safety of pharmacological interventions for managing sickle cell disease complications in children and adolescents: Systematic review with network meta-analysis

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Abstract

This study aimed to synthesize the evidence on the effects of disease-modifying agents for managing sickle cell disease (SCD) in children and adolescents by means of a systematic review with network meta-analyses, surface under the cumulative ranking curve (SUCRA) and stochastic multicriteria acceptability analyses (SMAA) (CRD42022328471). Eighteen randomized controlled trials (hydroxyurea [$n = 7$], L-arginine [$n = 3$], antiplatelets [$n = 2$], immunotherapy/monoclonal antibodies [$n = 2$], sulfates [$n = 2$], docosahexaenoic acid [$n = 1$], niprisan [$n = 1$]) were analyzed. SUCRA and SMAA demonstrated that hydroxyurea at higher doses (30 mg/kg/day) or at fixed doses (20 mg/kg/day) and immunotherapy/monoclonal antibodies are more effective for preventing vaso-occlusive crisis (i.e., lower probabilities of incidence of this event; 14, 25, and 30%, respectively), acute chest syndrome (probabilities ranging from 8 to 30%), and needing of transfusions (11–31%), while L-arginine (100–200 mg/kg) and placebo were more prone to these events. Therapies were overall considered safe; however, antiplatelets and sulfates may lead to more severe adverse events. Although the evidence was graded as insufficient and weak, hydroxyurea remains the standard of care for this population, especially if a maximum tolerated dose schedule is considered.

KEYWORDS
adolescents, children, disease-modifying agents, meta-analysis, sickle cell disease, systematic review

1 | INTRODUCTION

Sickle cell disease (SCD), a group of inherited blood disorders marked by mutations in the beta-globin chain of hemoglobin (hemoglobin S—HbS) that leads to chronic hemolytic anemia, affects over 3 million people globally, with an annual meta-estimated birth prevalence of 300,000 children—with 80% of this population living in sub-Saharan Africa.[1,2] SCD is currently recognized as a global public health concern, being the leading cause of pediatric stroke,[3,4] whose other common permanent sequelae that significantly impair patients' quality of life include vaso-occlusive crises (VOC), acute chest syndrome (ACS), and end-organ damage that occur across the lifespan.[3–5] SCD is also associated with premature death (median age 43 years; 31.5–55.0 years),[6] with estimated under-5 mortality from the disease of over 50% in some regions.[7]

Abbreviations: ACS, acute chest syndrome; AS, sickle cell trait; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HbSS, homozygous for the sickle cell disease; HU, Hydroxyurea; NMA, network meta-analysis; OR, odds ratio; RCT, randomized controlled trial; RoB 2.0, Cochrane Collaboration Risk of Bias of studies of interventions; SC411, highly purified docosahexaenoic acid ethyl ester formulation with a proprietary delivery platform; SCD, sickle cell disease; SD, standard deviation; SMAA, stochastic multicriteria acceptability analyses; SUCRA, surface under the cumulative ranking curve analyses; USA, United States of America; VOC, vaso-occlusive crisis.

The SCD management is complex and requires early diagnosis, prevention of complications and end-organ damage.[8,9] Therapeutic options for this disease are still limited, especially for the pediatric population, and current clinical practice guidelines are not straightforward for selecting therapies for this population.[10–12] Although recent pipelines in the context of clinical trials demonstrated promising results with gene therapies toward the cure of SCD, bone marrow or stem cell transplantations are the only available curative approaches for these patients.[13] Other nonpharmacological treatments as chronic blood transfusions can also be used to reduce symptoms; yet, these procedures are associated with several barriers including patients' eligibility, treatment access, costs, and related complications (e.g., abnormally high levels of iron in the blood, reactions due to a mismatch between donors and recipients).[14,15]

According to Tambor et al.,[15] some pharmacological interventions collectively termed as "disease-modifying therapies," intended to prevent or reduce the occurrence of SCD-related symptoms and complications and to improve long-term outcomes, are globally available. Hydroxyurea (HU) (a ribonucleotide reductase inhibitor), the most common drug used in this scenario, was initially developed and approved in 1967 by the north American agency Food and Drug Administration (FDA) as an antineoplastic agent (doses of 20–30 mg/kg/day or 80 mg/kg every 3 days) to treat some conditions as myeloproliferative syndromes—leukemia, melanoma, and ovarian cancer. The diverse set of mechanisms of action of HU—including the drug's ability to increase fetal hemoglobin levels, decrease the quantity of leukocytes and reticulocytes in circulation, and modify adhesion molecules and vasodilation, led to FDA approval for the treatment of SCD in 1998 at lower doses (usually starting at 15–20 mg/kg/day, with dose escalation to a maximum tolerated dose of 30–35 mg/kg/day). While HU is a mainstay in SCD, its original indication for a variety of cancers has been discontinued over the past decades due to advancement on new target therapies (e.g., tyrosine kinase inhibitors) in oncology. HU is currently reserved as an option for chronic myeloid leukemia.[8,16,17]

Nonetheless, although studies in SCD show significant reductions in acute complications due to fetal hemoglobin induction, HU does not appear to protect against long-term cardiopulmonary disorders.[8] Besides this drug, other disease modifying agents, such as L-glutamine (indicated for patients aged 5 years and older), voxelotor (indicated for patients aged 12 years of and older), and crizanlizumab (indicated for patients aged 16 years of and older), were recently approved (2017–2020) by regulatory agencies as further options to manage SCD complications.[16,18,19] Other interventions as monoclonal antibodies and immunoglobulins are still of off-label use.

With this overdue increase in the pipeline for SCD therapies in recent years, it is important to ensure a robust body of evidence on the efficacy and safety of these interventions, aiming at supporting more assertive decision-making processes in clinical practice. However, updated comparative evidence on the effects of disease-modifying therapies for SCD comes primarily from systematic reviews with meta-analyses limited to adult patients[20,21] or focused only on some selected therapies, curative approaches or prophylactic measures[22–26]; with few of them performing network meta-analyses (NMA)—a technique that enables to simultaneously compare the effects among multiple treatments in one single model, including both direct (i.e., based on existing comparative studies in the literature) and indirect (i.e., based on common comparators) evidence.[27–29]

Thus, given these literature gaps, we aimed to synthesize and critically appraise the evidence on the clinical effects of the available drugs for managing SCD complications in children and adolescents by means of a broad systematic review with NMA and stochastic multicriteria acceptability analysis (SMAA).

2 | METHODS

This study was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, Network Meta-analysis extension guidelines and Cochrane Collaboration recommendations[30–32] (PROSPERO registration: CRD42022328471). The protocol has been published[33] and is available online for consultation at Open Science Framework (DOI: 10.17605/OSF.IO/CWAE9). Two authors independently conducted all steps of the studies' selection and data extraction. A third author was consulted in case of discrepancies.

2.1 | Search strategy and eligibility criteria

The following electronic databases were searched for references of clinical trials: PubMed, Scopus, and Web of Science, with no data or language restrictions (updated on May 31, 2022). Trial registration databases (clinicaltrials.gov) and the reference lists of the included studies were also searched as part of manual searching process (see complete search strategy in Supplemental Material 1).

Titles and abstracts of the retrieved articles were screened for eligibility. Relevant records were then read in full and primary studies that met the following inclusion criteria (PICOS' acronym) were included for data extraction and analyses:

- Population: studies evaluating children or adolescents (<19 years old) diagnosed with SCD, previously treated or untreated;
- Interventions: studies assessing any pharmacological intervention (i.e., drugs) intended to prevent or reduce the occurrence of SCD-related symptoms and complications, used alone or in combination with other therapies, in any regimen or schedule. These interventions can be broadly referred as disease-modifying therapies[15];
- Comparator: studies with any pharmacological intervention or placebo;
- Outcomes: studies assessing at least one of the following outcomes, adapted from the minimum core outcome set for SCD from Tambor et al.[15]: number of deaths, VOC (acute sickle cell pain frequency, duration, intensity), ACS, frequency of hospitalization and length of hospital stay, need for blood transfusion, Hb levels and other laboratory parameters, safety (incidence of serious adverse events, most common adverse events, drugs' discontinuation/tolerability);
- Study design: randomized controlled trials (RCT).

Studies on curative approaches (i.e., transplantation, gene therapy); nonpharmacological treatments (i.e., blood transfusions), supportive care with analgesics or complementary medicine; studies on prophylaxis, parasite reduction ratio or malaria incidence/prevalence; other study designs; articles assessing only economic outcomes or articles in non-Roman characters were excluded.

2.2 | Data extraction and methodological quality assessment

A standardized form (Microsoft Excel, Redmond, WA) was used to extract information on: articles' general data (authors, year of publication, country, sample size); participants' characteristics (age, sex, diagnosis); details of the intervention and controls (drugs, regimen); clinical outcomes results. The methodological quality of the included studies was evaluated using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials of interventions—RoB 2.0.[30] This tool incorporates the evaluation of the following sources of bias per outcome: selection, performance, detection, attrition, and reporting bias. Evidence was finally judged as with low risk of bias, some concerns or high risk of bias.

2.3 | Statistical analyses

A narrative synthesis of the findings from the included studies, structured around the type of intervention, target population, and type of outcome is provided in tables.

Additionally, NMA, an approach recommended by the International Society for Pharmacoeconomics and Outcome Research,[27,34] was performed for each outcome of interest. To obtain the pooled effect sizes (i.e., odds ratio—OR) of treatment comparisons, a random-effect model based on the Markov Chain Monte Carlo simulation method (i.e., Bayesian approach) was used (burn-in of 20,000 iterations; 50,000 iterations).[35,36] Transitivity analyses to verify potential between-trial heterogeneity were performed by comparing population, interventions, comparator, and outcome definitions among studies. At the end, a standard heterogeneity parameter was assumed for all comparisons. A consistency model was built for each outcome of interest, and the treatments' relative effect sizes were reported as OR with 95% credibility intervals. A conservative analysis of noninformative priors was used. Both fixed and random effect models were tested; the one with the lowest deviance information criteria (goodness-of-fit) was selected. Convergence was attained based on visual inspection of Brooks–Gelman–Rubin plots and potential scale reduction factor ($1 < PSRF \leq 1.05$). Ranking probabilities were calculated by surface under the cumulative ranking analysis (SUCRA) for each outcome of interest in order to increase the estimated precision of the relative effect sizes of comparisons and to properly account for correlations between multiarm trials.[34,37] To estimate the robustness of the networks, inconsistency, defined as the difference between the pooled direct and indirect evidence for a particular comparison, node-splitting analysis were performed. In this approach, the evidence on a specific node (the split node) is tested (p values < 0.05 reveal significant inconsistencies in the network).[38] The geometry of the networks was assessed according to Tonin et al.[39] Sensitivity analysis to evaluate the impact of the individual studies on the meta-analyses (i.e., between-trials heterogeneity) and subgroup analyses according to patients' age group (>10 years vs. <10 years) and region of study's origin (North America vs. Africa) were performed whenever possible.[40]

Analyses were performed in Addis version 1.16.6 (Aggregate Data Drug Information System; http://drugis.org/index) and confirmed in R/RStudio (gemtc package). Network plots were built in Gephi 0.9 (Fruchterman-Reingold algorithm) (https://gephi.org).

2.4 | Multicriteria analysis

A SMAA, an extension of the multicriteria decision analysis was also performed. This decision-making tool enables to estimate the benefit/risk ratio of interventions. "Benefit" is described as the effect that takes the patient from the disease condition to health, while "risk" refers to an effect that leads the patient from health to disease. It simultaneously evaluates multiple therapeutic efficacy and safety attributes, finally providing a "rank" of the treatments, ranging from the worst to the best clinical option.[41–43]

The SMAA was used to determine the benefit/risk ratio of the disease-modifying therapies in SCD using evidence from the NMA of clinical trials with unknown or partially known preferences of the outcomes. Given the reduced number of studies reporting all the outcomes of interest and aiming at including the highest number of treatments in the analyses, three risk criteria (i.e., the most reported) were initially considered in the scenario I: VOC, ACS, and serious adverse events. A model with missing preferences (i.e., without a previously established order of importance for the three outcomes) was built to provide a brief overview of the evidence. In a following step, additional models considering preferred order for the outcomes to occur were built as part of the sensitivity analyses. HU 20 mg/kg was considered the baseline treatment in scenario I as it is the most used drug in daily practice for these patients (fixed dose).[8,44,45] An alternative scenario (scenario II) using placebo as a baseline comparator was also built. Models were created using Monte Carlo iterations in Addis version 1.16.6 (Aggregate Data Drug Information System; http://drugis.org/index).

2.5 | GRADE

The certainty of the evidence at the outcome level was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[46] Outcomes for a given comparison were rated as high quality and then downgraded based on five main criteria (risk of bias, imprecision, indirectness, heterogeneity, publication bias). The main comparator was fixed as HU 20 mg/kg as it is the standard active treatment in daily practice for this population.[8,44,45]

3 | RESULTS

The search strategy retrieved 895 records after duplicates removal, of which 834 were excluded during the screening process. Forty records were excluded after full-text appraisal (a complete list of excluded studies is available in Supplemental Material 2), remaining 21 records for data extraction and analyses referring to 18 RCTs (see flowchart in Supplemental Material 3).[44,45,47–65] No additional study was found through manual searches. It is important to disclosure that results from the BABYHUG trial (NCT00006400) were published in three different articles,[44,50,51] while data from the NCT02961218 is available in two publications.[45,59] The NOHARM trial (NCT01976416) was published in 2017 by Opoka et al.[56]; at the end of this study, children were prescribed HU (20 mg/kg/day) some months before enrolling the NOHARM MTD trial (NCT03128515), a dose-escalation study in which this population was randomly assigned (1:1) to receive HU at a fixed standard dose (20 mg/kg/day) or to escalate therapy to a maximum tolerated dose (initial dose 25 ± 5 mg/kg/day; mean dose around 30 mg/kg/day; escalation allowed every 2 months at a maximum of 35 mg/kg/day).[65] The main characteristics of the included studies are presented in Table 1. A summary table of the characteristics of these therapies (e.g., mechanism of action, indication) is depicted in Supplemental Material 4.

These 18 trials (n = 2159 patients) were published between 1982 and 2022, being mostly conducted in one single country (especially from Africa [n = 8, 44.4%] and North America [n = 6, 33.3%]). Four studies were designed as multinational trials. Around one-third of the RCTs were restricted to homozygous patients for the SCD allele (HbSS); yet when reported (n = 4), patients with sickle cell trait (AS) represented less than 30% of the population. Males accounted for almost half of the patients with ages varying from 1 to 19 years. Treatment duration was variable, with n = 7 trials assessing outcomes until 6 months and other n = 8 with longer follow-ups (over 12 months). Almost all trials (n = 15, 83.3%) directly compared active drugs with placebo. The evaluated interventions (at different doses/schedule) were: HU (n = 7 trials), L-arginine (n = 3), antiplatelets (n = 2), immunotherapy/monoclonal antibodies (n = 2), sulfates (n = 2), docosahexaenoic acid (n = 1), niprisan (n = 1).

The overall methodological quality of the studies for the main outcomes of interest was judged as low-to-moderate (see Supplemental Material 5), with six trials (33.3%) presenting at least one outcome with a high risk of bias and other seven trials (38.9%) with one outcome with some methodological concerns. Conversely, nine studies (50.0%) had at least one outcome judged as with low risk of bias. All trials were randomized, although the randomization process and allocation concealment were properly described for all outcomes in around half of the studies. The remaining RCTs (n = 8, 44.4%) presented some concerns regarding the deviation of intended interventions as they had no published protocol or intention-to-treat was unclear; two trials were designed as single-blinded. For all studies, the outcomes of VOC, ACS, discontinuation, and incidence of serious adverse events were related to some concerns given their subjective measurement (i.e., some based on pain-related admissions). In eight trials (44.4%), some outcomes were presented as aggregated data (i.e., not according to patients' interventions subgroups), leading to some concerns on the domain of selection of reported results. Almost all trials (n = 17, 94.4%) declared to be funded; half of them by pharmaceutical companies; yet most authors declared no conflict of interest with the research. Further information on sponsors' role in the trial were only available for seven studies (38.9%), most of which (n = 5/7) declaring that funders did not participate in study design, data collection, data analysis, data interpretation, nor writing of the report (see complete statements in Supplemental Material 5).

We were able to build six major NMAs for ACS (n = 13 studies), VOC (n = 11 studies), need for transfusion (n = 9), hospital admission (n = 10), treatment discontinuation from any cause (n = 11), and incidence of serious adverse events (n = 9) (see Figure 1). All original networks were found to be robust within the transitivity analyses (no node-split analyses were possible given the reduced number of studies per comparison in a node). The geometry of the networks confirmed the limited available evidence for most comparisons (open networks, few included studies) (see Supplemental Material 6). Except for the comparison of HU 10 mg/kg/day versus maximum tolerated dose (30 mg/kg/day) showing higher doses statistically associated with fewer incidence of ACS (OR 0.04 [95% CrI 0.01–0.65]), no significant statistical differences among treatments were found neither in the original analyses (accounting for all treatments) nor in the sensitivity analyses with the hypothetical removal of the NOHARM MDT study (i.e., continuation of the NOHARM trial; only dose-escalation trial) or by patients' age and region of origin. See complete consistency analyses in Supplemental Materials 7 and 8.

Considering SUCRA (Figure 2), higher doses of HU (both maximum tolerated doses of around 30 and 20 mg/kg/day) and monoclonal antibodies/immunotherapy (canakinumab or immune globulin) exhibited lower probabilities of ACS incidence (values of 8, 29, and 22%, respectively), VOC (14, 30, and 25%, respectively), and need for transfusions (11, 31, and 32% respectively) (i.e., potentially more effective treatments regarding these events). HU 30 and 20 mg/kg/day were also associated with lower hospital admission rates (probabilities of around 10 and 25%, respectively). Conversely, patients on placebo were more prone to hospital admissions (around 60% probability), transfusions (68%), and VOC (around 70%). L-Arginine (any dose) and lower doses of HU (10 mg/kg/day) were related to higher ACS incidence rates. Although therapies were overall considered safe (few reported adverse events), the use of antiplatelet and sulfates ($MgSO_4$) can lead to more discontinuations (70–80%) and serious adverse events (over 50%).

For other outcomes, including death from any cause, length of hospital stay, and some laboratory parameters results were briefly summarized in Supplemental Material 9. No meta-analyses were performed given the scarcity of data and lack of standardized report of these outcomes.

Results of SMAA were similar to the ones obtained by individual NMAs. The acceptability rank of scenario I (ACS, VOC, and serious

TABLE 1 Characteristics of the included trials ($n = 18$)

Publication (author, year)	Study (trial)	Design	Country*	Patients**	Intervention control	*N*	Age#	% Male	Treatment duration	Mean follow-up	Primary outcome¥
Gail 1982	–	Double-blind	Ghana	HbSS	Urea 0.266 g/kg Placebo	40 39	<5–14 y	49.0	6 months	14 months	Not defined
Ferster 1996	–	Single-blind, cross-over	24 African countries	HbSS	HU 20 mg/kg/day Placebo	22 22	9.0 y (2–20)	48.0	6 months	14 months	Hospital admission
Wambebe 2001	–	Double-blind, cross-over, IIB	Nigeria	HbSS	Niprisan 12 mg/kg/day Placebo	33 36	15.4 y (SD 5.11)	43.9	6 months	14 months	VOC, pain
Wang 2011 Alvarez 2012 Thornburg 2012	BABY HUG—NCT00006400	Double-blind	USA	HbSS (98%)	HU 20 mg/kg/day Placebo	96 97	13.6 m (SD 2.7) 13.5 m (SD 2.8)	43.5	24 months	24 months	Organ dysfunction
Goldman 2013	–	Double blind	Canada	HbSS (60%); AS (27%)	IV $MgSO_4$ 100 mg/kg Placebo	51 53	12.4 y (SD 4.0) 12.4 y (SD 3.7)	46.0	–	9 months	Hospital length stay
Morris 2013	NCT01796678	Double-blind phase II	USA	HbSS (72%); AS (19%)	L-Arginine 100 mg/kg Placebo	28 29	13.9 y (SD 4.0)	48.0	–	6 months	Hospital length stay
Brousseau 2015	MAGiC—NCT01197417	Double-blind	USA	HbSS (93%)	IV $MgSO_4$ 40 mg/kg Placebo	101 103	13.4 y (SD 4.6) 13.8 y (SD 4.8)	48.5	–	3 months	Hospital length stay
Heeney 2016	DOVE—NCT01794000	Double-blind	Multinational	HbSS	Prasugrel 0.08 mg/kg Placebo	171 170	10.6 y (SD 4.3)	49.2	9 months	12 months	VOC, pain, ACS
Opoka 2017	NOHARM—NCT01976416	Double-blind	Uganda	HbSS	HU 20 mg/kg/day Placebo	104 103	2.2 y (SD 0.9)	54.0	12 months	12 months	Incidence of malaria
John 2020	NOHARM MDT NCT03128515	Double-blind	Uganda	HbSS	HU 20 mg/kg/day (fixed) HU ~30 mg/kg/day (MDT)	94 93	4.6 y (SD 1.0) 4.8 y (SD 0.9)	55.0	24 months	24 months	Hemoglobin and fetal hemoglobin levels
Daak 2018	SCOT—NCT02973360	Double-blind, phase II	USA	HbSS (80%); AS (15%)	SC411 20–60 mg/kg Placebo	50 17	11.8 y (SD 2.6) 12.6 y (SD 3.7)	52.4	9 months	22 months	DHA, EPA changes

(Continues)

TABLE 1 (Continued)

Publication (author, year)	Study (trial)	Design	Country*	Patients**	Intervention control	*N*	Age#	% Male	Treatment duration	Mean follow-up	Primary outcome¥
Hsu 2018	HESTIA1 - NCT02214121	Double-blind, phase II	Multinational	HbSS	Ticagrelor 0.125–0.75 mg/kg Placebo	17 8	11.2 y (3–17)	46.7	1 month	–	Platelet inhibition
Rees 2019 Rees 2022	NCT02961218	Double-blind	Multinational	HbSS; AS	Canakinumab 300 mg/dose Placebo	25 24	15.8 y (SD 2.69) 15.6 y (SD 3.28)	57.1	12 months	12 months	VOC, pain
Abdullahi 2020	SPRINT—NCT02675790	Single-blind, phase III	Nigeria	HbSS; AS	HU 10 mg/kg/day HU 20 mg/kg/day	50 50	6.6 y	55.4	36 months	36 months	Incidence of stroke
Manwani 2020	NCT01757418	Double-blind, phase II	USA	HbSS (95%)	Immune globulin 400 mg/kg Placebo	18 19	14.4 y (SD 3.58) 13.8 y (SD 3.90)	53.8	1 month	1 month	VOC, pain
Onalo 2021	–	Double-blind, phase II	Nigeria	HbSS; AS	L-Arginine 100 mg/kg Placebo	35 33	10.7 y (SD 3.2) 10.5 y (SD 3.5)	56.0	1 week	1 month	Analgesic usage
Abdullahi 2022	SPRING—NCT02560935	Double-blind, phase III	Nigeria	HbSS (85%)	HU 10 mg/kg/day HU 20 mg/kg/day	109 111	7.4 y (5.4–9.6) 7.0 y (5.5–8.4)	48.5	36 months	36 months	Incidence of stroke
Reyes 2022	NCT02536170	Double-blind	Nigeria	HbSS (65%); AS (25%)	L-Arginine 100 mg/kg L-Arginine 200 mg/kg Placebo	36 36 36	12.6 y (SD 3.8)	48.0	1 week	1 month	Opioid usage

*Multinational trials took place in more than 10 countries (North America, Europe, Africa, Middle-East).

**Most patients were homozygous for sickle cell disease; few presented heterozygous genotype. Cases of Sβ0-Thalassemia were reported in Wang 2011 (2%), Goldman 2013 (9%), Morris 2013 (9%), Daak 2018 (<5%). The studies from Brousseau 2015, Heeney 2016, Hsu 2018, Rees 2019 lack on presenting the rates for Sβ0-Thalassemia patients.

#Patients' age as reported by authors (mean with SD or range); some studies reported data for the entire sample (no differences among intervention vs. control groups).

¥Primary outcome as defined in the trial.

AS, sickle cell trait; DHA, ν-3 fatty acid docosahexaenoic; EPA, eicosapentaenoic acid; HU, hydroxyurea; HbSS, homozygous for the sickle cell disease; MDT, maximum tolerated dose; SD, standard deviation, SC411, highly purified docosahexaenoic acid ethyl ester formulation with a proprietary delivery platform; USA, United States of America.

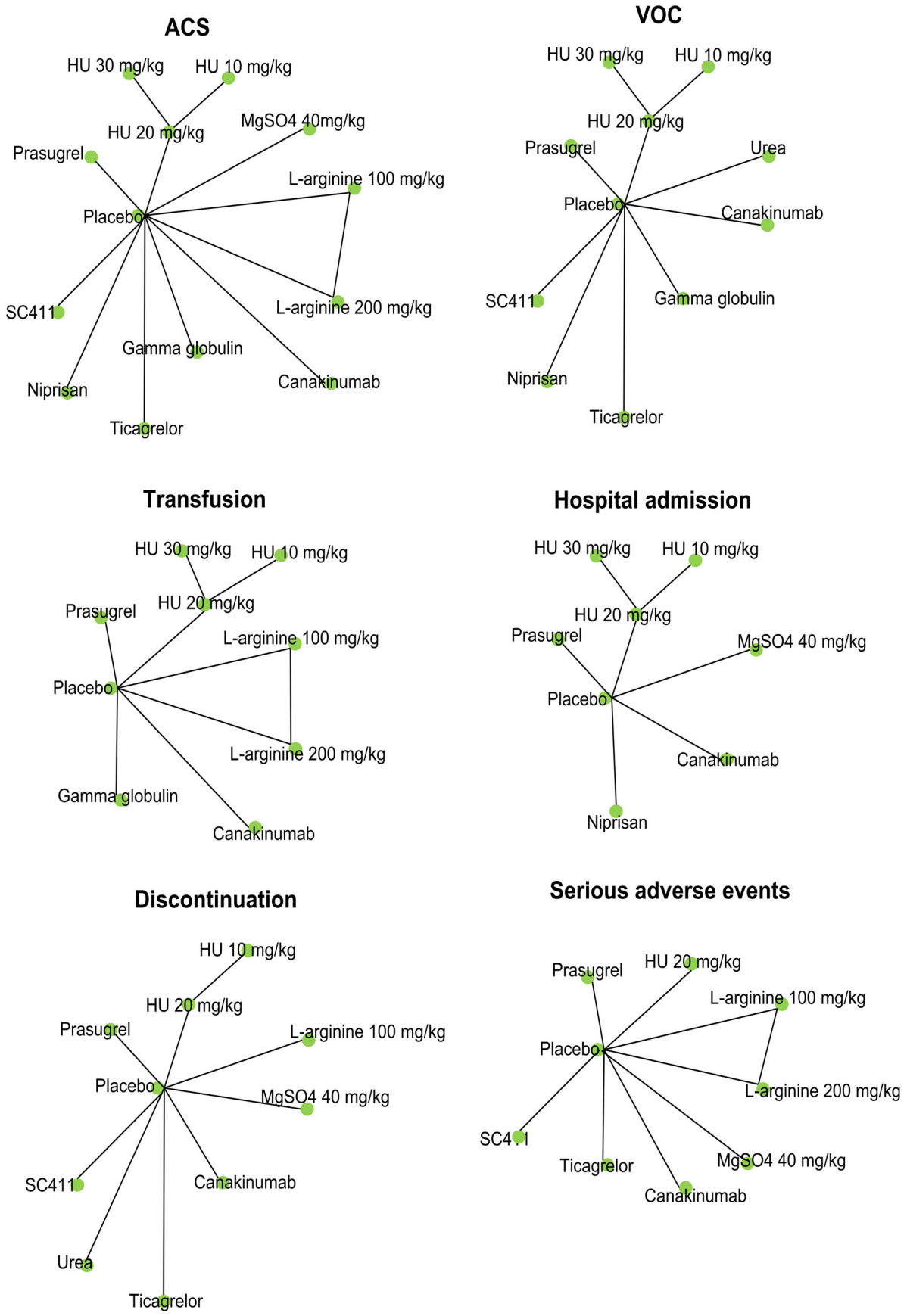
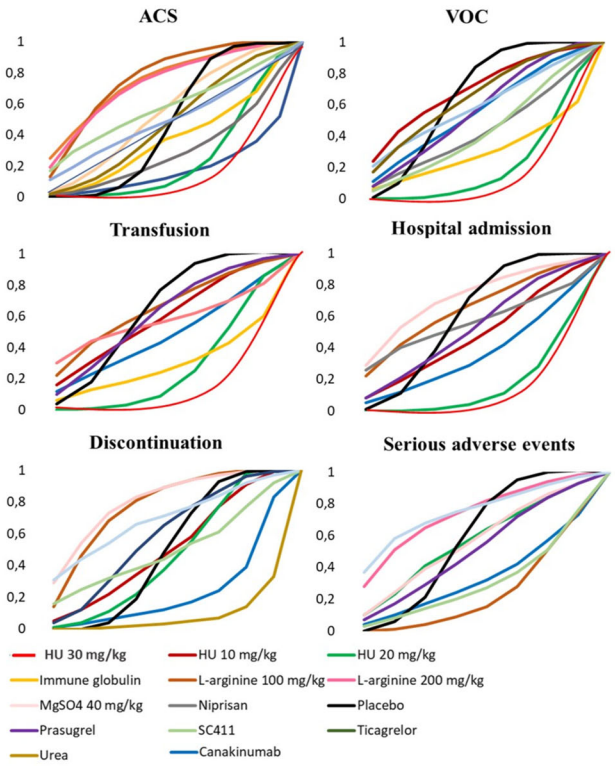


FIGURE 1 Network plots for the main outcomes of interest. Each circle (node) represents an intervention and lines represent direct comparisons.



Drug	ACS	VOC	Transfus	Hospital admission	Discontinuat	SAE
Canakinum	22%	55%	50%	40%	22%	32%
HU 10 mg/kg	76%	61%	61%	52%	49%	--
HU 20 mg/kg	29%	25%	32%	25%	45%	55%
HU 30 mg/kg	8%	14%	11%	9%	--	--
Immune globulin	42%	30%	31%	--	--	--
L-arginine 100 mg/kg	78%	--	70%	67%	77%	23%
L-arginine 200 mg/kg	75%	--	57%	--	--	73%
MgSO4 40 mg/kg	58%	--	--	75%	80%	55%
Niprisan	32%	43%	--	60%	--	--
Prasugrel	50%	58%	65%	57%	58%	50%
Ticagrelor	55%	63%	--	--	68%	74%
SC411	60%	48%	--	--	50%	30%
Urea	--	66%	--	--	7%	--
Placebo	52%	67%	68%	63%	48%	57%

FIGURE 2 Surface under the cumulative curve analyses (SUCRA) for the outcomes of interest. Higher probabilities are more associated to the occurrence of the event (i.e., negative outcomes). ACS, acute chest syndrome; VOC, vaso-occlusive crisis; HU, hydroxyurea; SAE, severe adverse events; SC411, highly purified docosahexaenoic acid ethyl ester formulation with a proprietary delivery platform.

adverse events criteria with missing preferences and HU 20 mg/kg as baseline alternative) is shown in Figure 3A (comprising seven therapeutic options and placebo). This scenario favored the use of HU maximum tolerated dose—30 mg/kg (central weight benefit–risk ratio of 68%) followed by HU fixed dose—20 mg/kg and immunotherapy/monoclonal antibodies (canakinumab). Placebo and antiplatelets (ticagrelor, prasugrel) were disadvantaged options (ratios less than 5%). When establishing ordinal preferences of the three criteria (VOC as the first important outcome followed by ACS and then and serious adverse events), results remained similar, with HU 30 mg/kg ranking first (central weight benefit–risk ratio of 57%), followed by HU 20 mg/kg and canakinumab (rates around 20%). Placebo and antiplatelets were again the worst options (<%). Similar findings were obtained in scenario II (Figure 3B) when using placebo as baseline for the same risk criteria (ACS, VOC, and serious adverse events), both in the missing preferences and ordinal preferences models (HU 30 mg/kg exhibited the best benefit–risk ratio [around 50%] followed by HU 20 mg/kg and canakinumab [around 20–25%] while placebo and antiplatelets ranked last).

The certainty of the evidence (GRADE approach) for the comparisons of the different therapeutic regimens versus HU fixed dose (20 mg/kg) varied from very low to moderate certainty for all outcomes of interest, especially due to the low methodological quality of the trials (i.e., lack of standard measures and report of outcomes), the small number of available studies (i.e., poor direct evidence), and the imprecision of some results (i.e., large credibility intervals) (see Supplemental Material 10).

4 | DISCUSSION

This systematic review with NMA and SMAA synthesized the available evidence from 18 RCTs about the profile of seven classes of disease-modifying therapies, resulting in 15 therapeutic approaches for managing SCD in children and adolescents. The global burden of SCD in this population, especially in patients under five years old, is currently well recognized, with pooled estimated mortalities of around 0.64 per 100 years of child observation (95% CI = 0.28–1.00).[66] Besides the negative impacts of the disease on patients' and family/caregivers' health-related quality of life,[67,68] SCD is associated with important economic burden, with estimates of average total cost of care per patient-month of over USD 2000.[69] This scenario led to the increase in the pipeline of new SCD therapies in the past years, including both disease-modifying therapies and curative approaches.[70] However, these are not yet widely available and may be associated with several challenges for pediatric use. Additionally, clinical practice and treatment guidelines for SCD are unclear or lack on recommendations for selecting these therapies.[10–12]

Few updated meta-analyses comparing the effect of disease-modifying therapies for SCD in the pediatric population exist, none of

(A) Scenario I

Alternatives	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Central weight
Canakinumab	9%	15%	17%	17%	14%	12%	11%	6%	7%
HU 20 mg/kg	5%	32%	31%	18%	9%	3%	2%	0%	7%
HU 30 mg/kg	62%	19%	8%	4%	2%	2%	1%	0%	68%
Niprisan	15%	16%	14%	12%	8%	7%	10%	19%	12%
Prasugrel	2%	5%	10%	15%	18%	18%	20%	12%	2%
Ticagrelor	2%	4%	6%	7%	8%	11%	19%	42%	2%
SC411	5%	10%	13%	15%	14%	13%	16%	14%	5%
Placebo	0%	0%	2%	11%	27%	34%	21%	5%	0%

Final rank	1	2	3	4	5	6	7	8
	HU 30 mg/kg	HU 20 mg/kg	Canakinumab	SC411	Prasugrel	Niprisan	Ticagrelor	Placebo

(B) Scenario II

Alternatives	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Rank 7	Rank 8	Central weight
Canakinumab	9%	15%	17%	16%	13%	11%	12%	7%	10%
HU 20 mg/kg	6%	27%	24%	16%	9%	7%	7%	5%	7%
HU 30 mg/kg	53%	20%	10%	5%	4%	3%	3%	1%	57%
Niprisan	20%	15%	13%	10%	7%	7%	10%	18%	20%
Prasugrel	3%	7%	12%	16%	16%	18%	17%	11%	3%
Ticagrelor	2%	4%	5%	7%	8%	10%	20%	42%	2%
SC411	7%	12%	15%	14%	13%	12%	15%	13%	6%
Placebo	0%	1%	4%	16%	30%	31%	16%	3%	0%

Final rank	1	2	3	4	5	6	7	8
	HU 30 mg/kg	HU 20 mg/kg	Canakinumab	SC411	Prasugrel	Niprisan	Ticagrelor	Placebo

FIGURE 3 Rank acceptability's from the stochastic multicriteria acceptability analysis. Each intervention has a probability of being the best treatment (rank 1) or the worst treatment (rank last) considering overall its benefits and risk (VOC, ACS, serious adverse events) (missing preferences models). Scenario I, HU 20 mg/kg as baseline; Scenario II, placebo as baseline.

them as NMA. Frimpong et al.[24] compared the safety and effectiveness of antimalarial therapy used for prophylaxis in children with SCD, while Gwaram et al.[71] evaluated the daily use of penicillin for preventing infections in this population, and Núñez et al. and Strouse et al. evaluated the impacts of using HU.[22,72]

In our NMA, practically no statistical differences among therapies for the outcomes of interest were found probably due the low number of included studies and data uncertainty regarding incidence of events (e.g., wide credibility intervals). However, SUCRA and SMAA revealed that HU at maximum tolerated doses (around 30 mg/kg/day), followed by fixed doses of this drug (20 mg/kg/day) and immunotherapy/monoclonal antibodies are potentially more effective for preventing ACS and VOC. They were also less associated with the need for blood transfusion and hospital admissions.

Since publication of its landmark trial in 1995, HU continues to represent a mainstay of disease-modifying therapy for SCD,[73–74] with evidence showing VOC rates' reduction by 50%.[8] This drug, a ribonucleotide reductase inhibitor, reduces the likelihood of hemoglobin S polymerization by inducing fetal hemoglobin production through stress erythropoiesis, decreasing inflammation and cell adhesion.[17,75] In 2020, the results of the NOHARM-MTD trial (NCT03128515),[65] an extension of the NOHARM study[56] (both included in our NMA) demonstrated that HU with dose escalation to the maximum tolerated dose (mean 29.5 ± 3.6 mg/kg/day; n = 94 patients) had superior clinical efficacy and equivalent safety to that of fixed-dose HU (mean 19.2 ± 1.8 mg/kg/day; n = 93 patients) with children presenting fewer incidence rate ratios of VOC (0.43 [95% CI, 0.34–0.56]), ACS (0.27 [95% CI, 0.11–0.56]), transfusions (0.30 [95% CI, 0.20–0.43]), and hospital admission (0.21 [95% CI, 0.13–0.34]). These results may address the next critical set of questions about drugs' optimal dosing in children with SCD, especially because although HU has a convenient once-daily dosing and is considered safe for the pediatric population (i.e., rare life-threatening clinical adverse events such as breathing problems, birth defects, cancer risk; some mild adverse events like nausea and vomiting), it requires further monitoring due of the risk of hematological adverse events (reports of neutropenia and thrombocytopenia in around 10–15% of patients), which can lead to underutilization rates due to poor medication adherence (around 30–40% of patients discontinue treatment due to blood abnormalities [yet, less than 1% of children will permanently discontinue treatment for drug-related issues]; overall good adherence rates are estimated to be less than 50%, based on pharmacy refills of

SCD children/adolescents).[73,76–78] Further barriers to the use of this drug in real-world settings can include provider- and system-related factors as drug access and costs.[75,76] Additionally, some patients may continue to have crises, end-organ damage, and decreased life expectancy despite the use of the drug (i.e., nonresponders), which contributes to drug underutilization.[79] Addressing patients and families concerns about medications, as well as routine assessment of adherence/beliefs and therapeutic monitoring, could help to overcome some of these utilization barriers.[80] Moreover, recent ongoing studies are assessing individualized pharmacokinetic-based dosing strategies for HU (NCT03789591), evaluating the underlying mechanisms and gut microbiome biomarkers potentially associated with HU efficacy,[81] assessing the feasibility of adding HU to simple transfusions for stroke prevention (NCT03644953), or repurposing other available agents aiming at fulfilling these gaps in clinical practice and improving patient outcomes.[16]

Monoclonal antibodies (canakinumab) or immunotherapies (intravenous immune globulin, pooled antibody, are already approved to treat other clinical conditions.[82,83] These big molecules were assessed as potential therapies for pediatric SCD, as they act on the inflammatory path of the disease and decrease neutrophil adhesion to endothelium and red blood cell-neutrophil interactions.[45,61] In our analyses, these treatments ranked among the most effective therapies, alongside with HU, which should be further evaluated in head-to-head, well-design and long-term RCTs for this population. Conversely, placebo and L-arginine (100–200 mg/kg) were more prone to therapeutic failure and should probably be avoided as mainstay approaches. Previous studies hypothesized that arginine therapy attenuates the endothelial damage of SCD by targeting nitric oxide metabolism and mitochondrial activity. However, no clinical benefits for pediatric patients based on the assessment of selected outcomes were observed for these drugs. It is possible that the doses of arginine were not sufficient to produce significant changes in the selected parameters or that this population does not respond to the intervention as adults with SCD.[84,85]

Although all therapies were overall considered safe (with few reported adverse events), the use of antiplatelet (prasugrel, ticagrelor) aiming at reducing the hypercoagulable state of SCD and inflammation, or the use of intravenous sulfates ($MgSO_4$—an inhibitor of K-Cl co-transport able to reduce dense sickle red blood cells)[86] were associated with more discontinuations and serious adverse events, which may limit their use in daily practice for children and adolescents—that is, considering their risk-benefit ratio.

The overall evidence synthesized in this study was found to be of low certainty for most outcomes, with closely balanced benefits and harms of the interventions, which may lead to conditional recommendations in clinical practice guidelines. Besides the small number of included studies (ranging from 1 to 2 for each comparison), most trials were judged as with poor-to-moderate methodological quality, especially due to the lack of standard measure and outcome reporting. These hampered further analyses, namely statistical comparisons between interventions for the outcomes summarized in Table 2 (e.g., death, length of hospital stay, and laboratory parameters). Tambor et al.[15] structured a core outcome set for disease-modifying therapies in clinical trials of SCD, which includes, among others, the report of ACS, blood transfusion, survival/mortality, and health-related quality of life. This set should be strictly followed by researchers and authors in the field because the harmonization of outcomes across interventional trials enables optimal appraisal of the evidence and valid decision-making process.

One should be aware that the decision of the best therapeutic approach for pediatric SCD in daily practice should consider, among other factors, patients' and family/caregivers' preferences, drugs' access, and costs.[8,16] Well-designed RCTs and comparative-effectiveness studies, such as head-to-head trials assessing new therapies (immunotherapies) and combination therapies (multimodal approaches, e.g., HU with L-arginine, HU with canakinumab) are still needed in this area. This is especially important given the accelerated approval of some drugs in the past years (e.g. voxelotor, crizanlizumab) that are now being advocated for younger patient populations without evidence from controlled trials. Additional high-quality, longitudinal studies to better understand the natural history of the disease and real-world treatment patterns, aiming at informing optimal screening for SCD-related complications, are also needed. Finally, conducting further risk-benefit analyses, as SMAAs, including patients and healthcare providers' perspectives, can ground more assertive clinical decisions.

Our study has some limitations. Few studies were included in the systematic review. Given the heterogeneity among trials (e.g., patients' age, geographical location, genetic profile) and lack of standard data report, few outcomes could be statistically analyzed. The included trials differed in terms of size, risk of bias, and external validity. We tried to avoid systematic errors by performing transitivity and sensitivity analyses (results were similar to the original analyses). Yet, these studies represent the available evidence on the effect of disease-modifying therapies for this population; our findings may foster the conduction of further trials targeting the most promising drugs. As with any other method, NMAs and SMAAs are not free of limitations. The validity of this approach depends on the distribution of relative treatment effect modifiers across comparisons. Treatment rankings and benefit–risk ratios should not be interpreted separately from the relative treatment effects.

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CONFLICT OF INTEREST STATEMENT

The authors declare to have no competing interests regarding this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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