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Comparative efficacy and safety of pharmacological interventions for managing sickle cell disease complications in children and adolescents: a systematic review with network meta-analyses

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Background and Objectives

Sickle cell disease (SCD), an inherited hemoglobinopathy characterized by anemia, severe pain, acute chest syndrome (ACS) and vaso-occlusive crisis (VOC), has important impact on morbidity and mortality worldwide, especially in the pediatric population (over 50% die before age of 5). Although few treatment options are available, new disease modifying therapies, intended to prevent or reduce SCD-related complications are under development [1-3]. Our aim was to synthesize the evidence on the efficacy and safety of interventions for managing SCD in this population.

Methods

A systematic review with searches in PubMed, Scopus, and Web of Science was performed (May-2022). Randomized controlled trials comparing disease modifying agents in SCD patients under 18 years old were included. For each outcome of interest, data were pooled by means of Bayesian network meta-analyses with surface under the cumulative ranking curve analyses (SUCRA) and stochastic multicriteria acceptability analyses (SMAA). Results were reported as odds ratio (OR) with 95% credibility intervals (CrI) (PROSPERO-CRD42022328471).

Results

Seventeen trials (1982-2022) mostly from African countries (41%) and North America (35%), assessing the effect of different interventions' regimens (hydroxyurea [n=6 trials], L-arginine [n=3], antiplatelets [n=2], immunotherapy/monoclonal antibodies [n=2], sulphates [n=2], docosahexaenoic acid [n=1], niprisan [n=1]) and placebo were included. No statistical differences among treatments were found for the main outcomes **(Fig 1)**. SUCRA and SMAA revealed that immunotherapy/monoclonal antibodies and hydroxyurea 20 mg/kg are potentially more effective against acute chest syndrome (17% and 24% probabilities, respectively), VOC (29% and 20%) and needing of transfusions (around 25%), while L-arginine (100-200 mg/kg) and placebo were more prone to these events **(Fig 2 and 3).** Therapies were overall considered safe; however, antiplatelet and sulfates may lead to more discontinuations and severe adverse events. Results were similar between age subgroups (<10 vs. 10-19 years).

Fig 1. Network plots for the main outcomes
Each node represents an intervention and lines represent direct comparisons

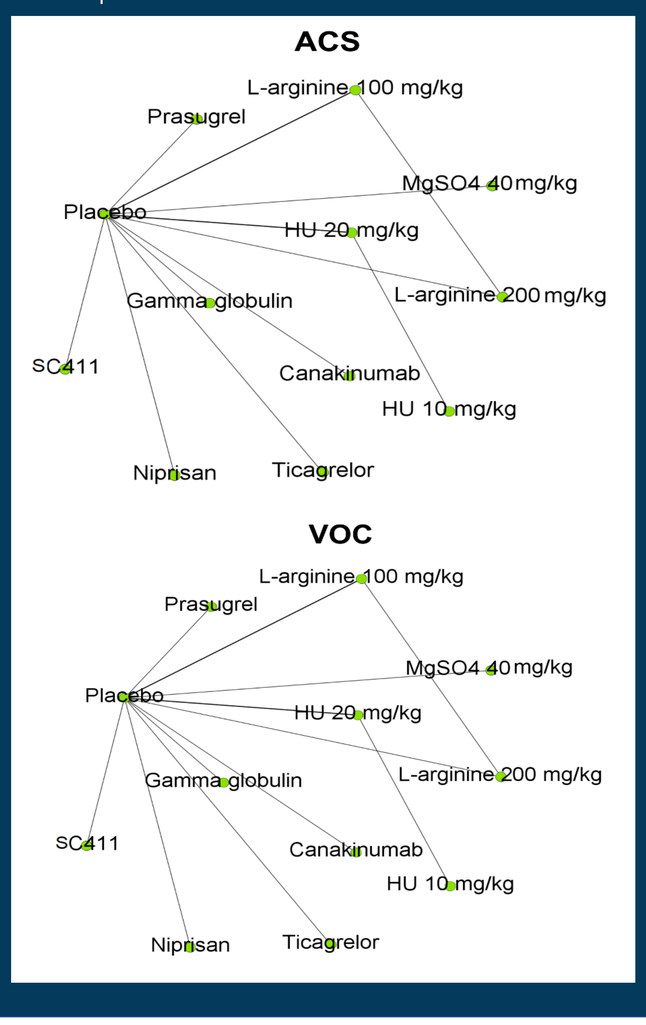
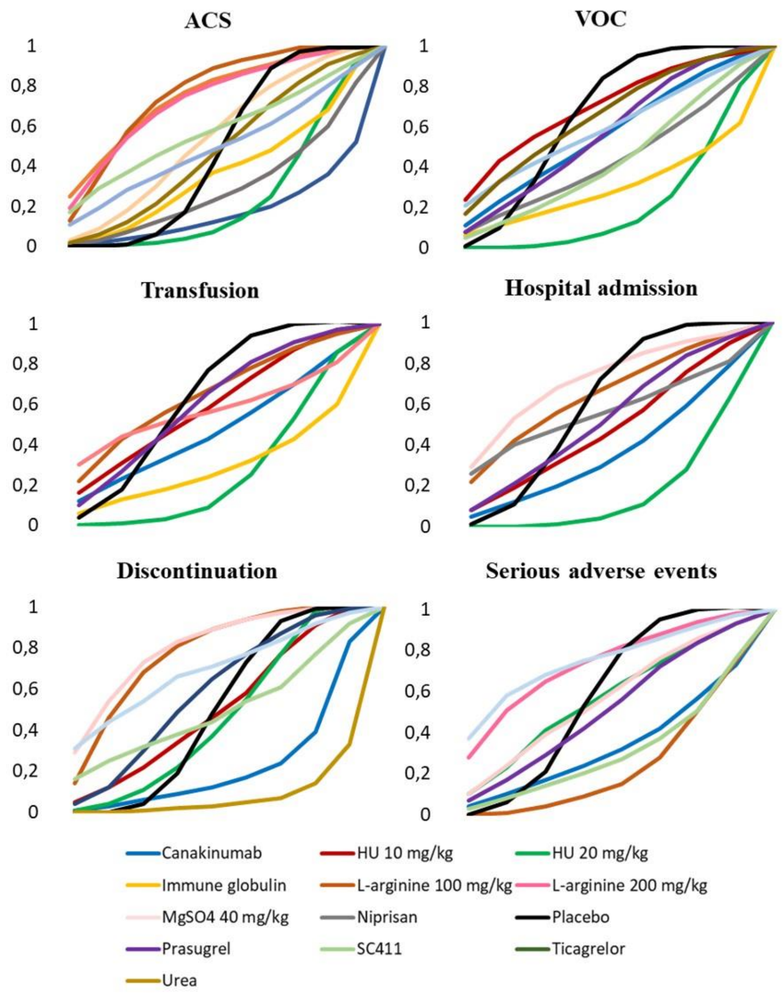


Fig 2. Surface under the cumulative curve analyses (SUCRA) for the outcomes of interest
Higher probabilities are more associated to the occurrence of the event (i.e., negative outcomes)



Drug	ACS	VOC	Transfus.	Hospital admission	Discontinuat.	SAE
Canakinum.	17%	50%	40%	35%	22%	32%
HU 10 mg/kg	74%	49%	58%	46%	49%	--
HU 20 mg/kg	24%	20%	25%	15%	45%	55%
Immune globulin	35%	27%	26%	--	--	--
L-arginine 100 mg/kg	75%	--	64%	64%	77%	23%
L-arginine 200 mg/kg	73%	--	56%	--	--	73%
MgSO4 40 mg/kg	54%	--	--	71%	80%	55%
Niprisan	30%	42%	--	55%	--	
Prasugrel	47%	56%	60%	51%	58%	50%
Ticagrelor	59%	58%	--	--	68%	74%
SC411	57%	48%	--	--	50%	30%
Urea	--	64%	--	--	7%	
Placebo	47%	67%	65%	59%	48%	57%

Fig 3. Rank acceptability's - Stochastic Multicriteria Acceptability Analysis (SMAA)
Each intervention has a probability of being the best treatment (rank 1) or the worst treatment (rank 6) considering overall its benefits and risk (VOC, ACS, serious adverse events) (missing preferences models). Scenario I: HU 20 mg/kg as baseline

Alternatives	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5	Rank 6	Central weight
Canakinumab	24%	22%	18%	14%	13%	10%	**23%**
HU 20 mg/kg	45%	30%	14%	6%	4%	1%	**55%**
Prasugrel	8%	15%	20%	19%	22%	17%	**8%**
Ticagrelor	7%	10%	10%	11%	16%	45%	**5%**
SC411	16%	18%	17%	13%	16%	19%	**14%**
Placebo	0%	5%	21%	37%	29%	7%	**1%**

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

Legend:
ACS: acute chest syndrome; HU: hydroxyurea; SAE: serious adverse event; SC411: docosahexaenoic acid; Transfus: need for transfusion; VOC: vaso-occlusive crisis

Conclusions

The available evidence on the effect of drugs for managing SCD in children and adolescents is insufficient and weak. No clear definition for some outcomes exists. Hydroxyurea may remain the standard of care for this population, however, long-term well-designed and well-reported trials comparing new immunotherapy/monoclonal antibodies should be performed.

References

[1] Brandow et al, J Hematol Oncol 2022; 15(1):20; **[2]** Quinn et al, Pediatr Blood Cancer 2022; 69(8):e29805; **[3]** Tonin et al, Pharm Pract (Granada) 2017; 15(1):943

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