Safety Assessment in Pediatric SLE: Challenges & Opportunities

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Outline

- Pediatric-specific safety considerations
- Safety data from pSLE
- Challenges of capturing rare events and strategies

What are the Safety Concerns in pSLE?

Short Term

- Infections
- Hypersensitivity reactions
- Side effects/tolerability
- Impact on growth

Long Term

- Growth and bone health
- Puberty and future reproductive health
- Central nervous system development
- Risk of malignancy

Risks governed by specific properties & mechanism of action of the medication in question

Is safety different in children?

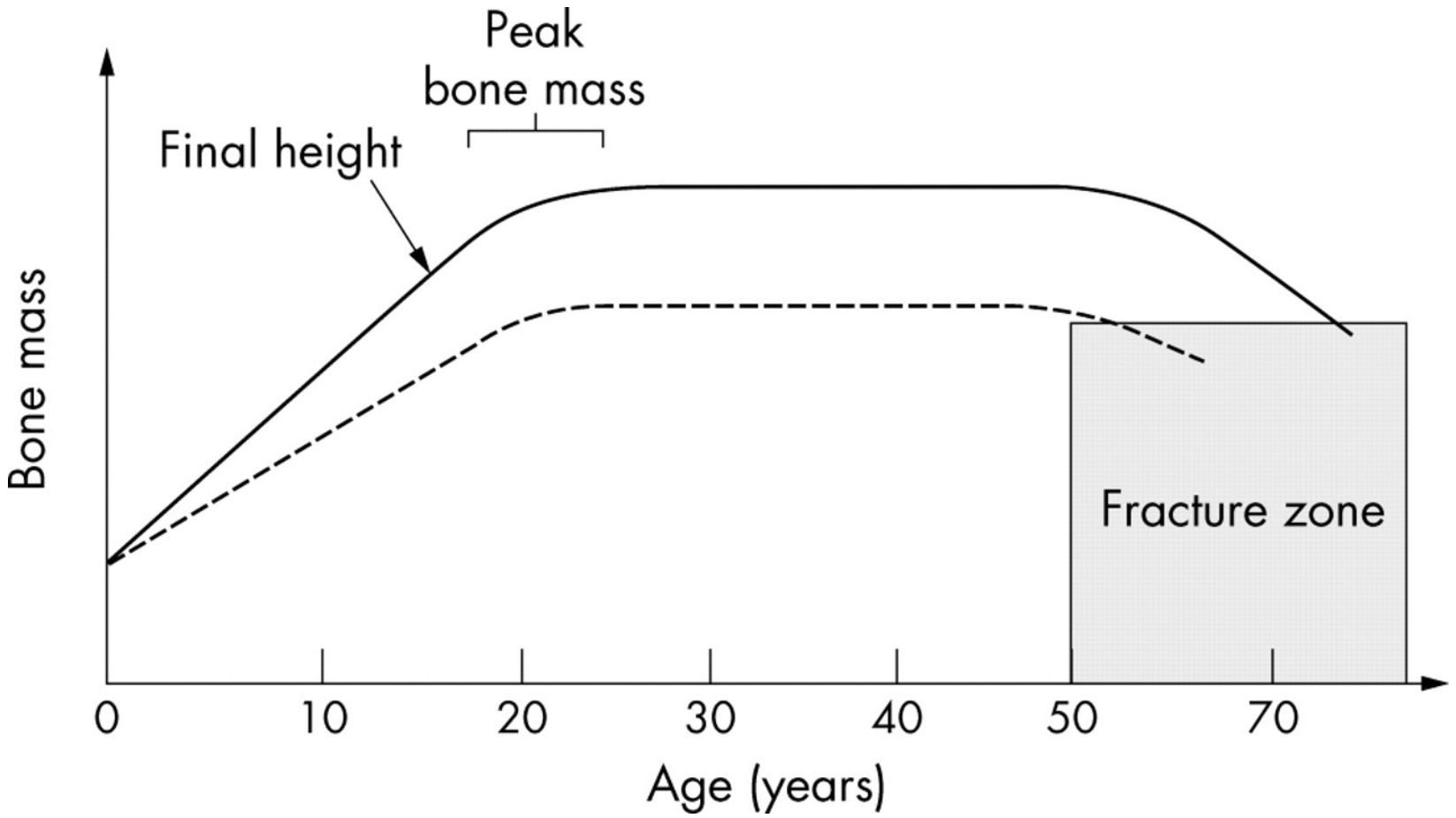
Children have lower baseline risks for infection and co-morbidities

Children have fewer concomitant medications because they are healthier on average

Children are still developing physically, neurologically and emotionally

Bone Health – Pediatric Considerations

- Majority of bone deposited in adolescence
- Peak bone mass achieved around 20 years of age
- Perturbation in PBM during childhood may lead to early osteoporosis and increased fractures



Glucocorticoids are the culprit in pediatric rheumatic disease

Davies Arch Dis Child 2005

Linear Growth and Puberty

In patients with pediatric lupus, clinicians should monitor for delayed pubertal onset and decreased growth velocity that can result from disease activity and glucocorticoid treatment and consider referral to pediatric endocrinology if indicated.

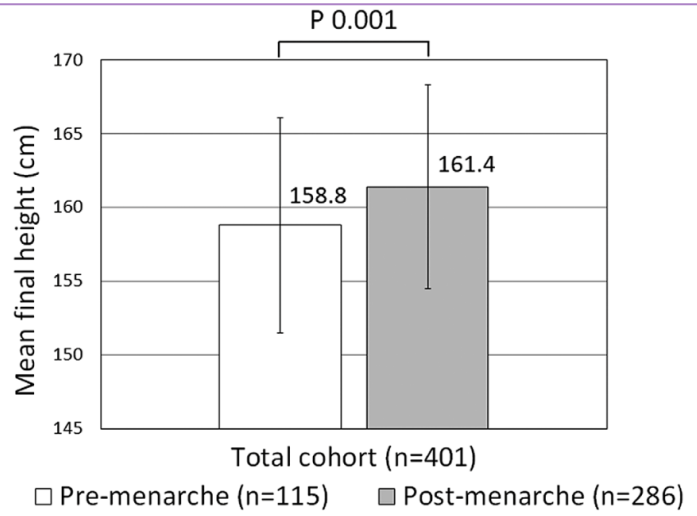


Figure 1. Means of final height of patients based on timing of childhood-onset systemic lupus erythematosus (SLE) diagnosis. Bar graph comparing the mean final height (cm) of patients diagnosed with childhood-onset SLE premenarche and postmenarche. Whiskers represent the SD. *P* value was calculated from an unpaired *t*-test.

Table 3 Pubertal characteristics of the 147/276 (53.3%) evaluable females with juvenile SLE

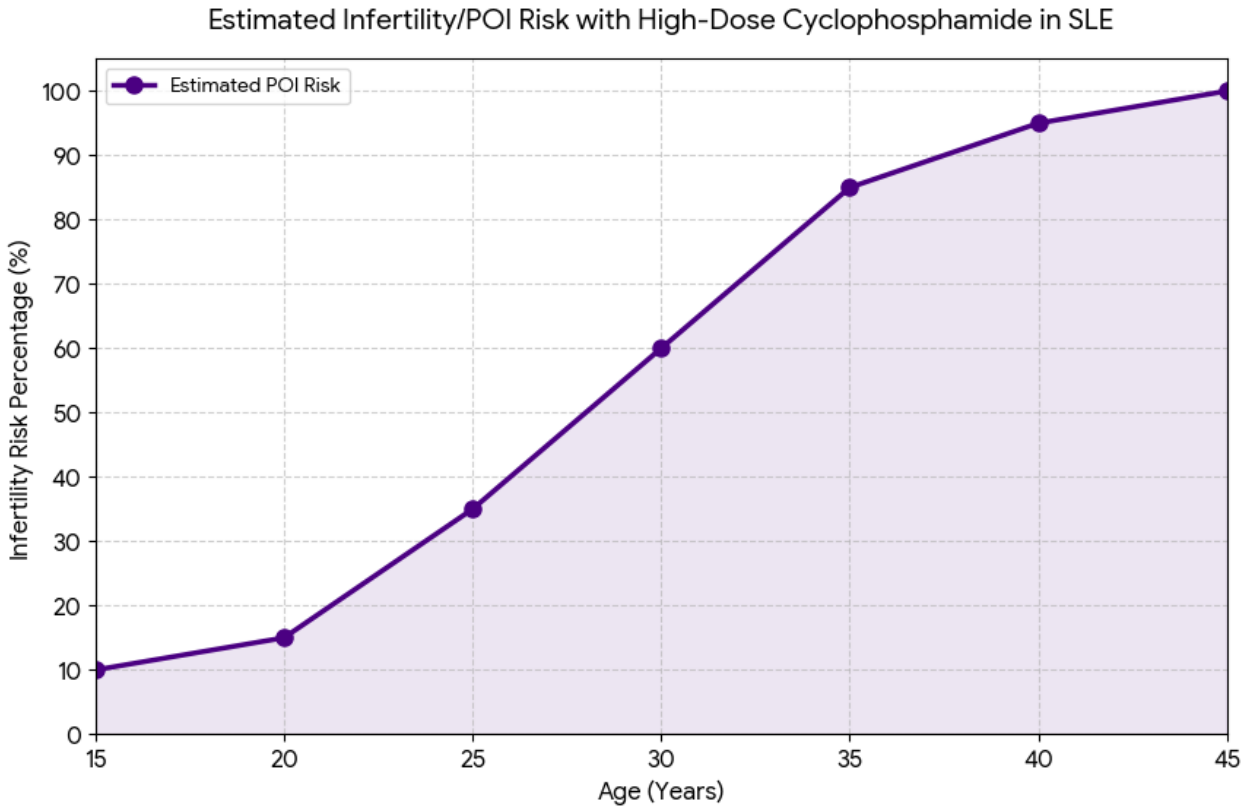
	Patients included for pubertal evaluation* (N=147)
Patients who had menarche registered, n	104/147 (70.7%)
Age at menarche, median (1st, 3rd quartile)	13.6 (12.6, 14.5)
Tanner ≥B2 at last visit	141/147 (95.9%)
Age at B2, median (1st, 3rd quartile)	11.9 (11.1, 12.7)
Delayed pubertal onset†	11/72 (15.3%)
Delayed pubertal tempo‡	37/96 (38.5%)
Delayed or absent menarche	25/114 (21.9%)
Delayed menarche§	15/114 (13.1%)
Absent menarche¶	10/114 (8.8%)
Normal menarche	89/114 (78.1%)
Delayed puberty**	53/147 (36.1%)
Irregular menses or postmenarche amenorrhoea	48/104 (46.2%)

DOSING OF GLUCOCORTICOIDS PREDICTED THESE OUTCOMES

Sontichai, *AC&R,* 2022 and Rygg, *ARD,* 2012

Differential Impacts of Treatment on Fertility: Cyclophosphamide

- Increased risk of ovarian failure risk by decade due to a loss of ovarian reserve
- Try to limit the cumulative dose of CYC the patient receives but pediatric patients may need multiple courses
- Increased use of the Euro-Lupus protocol



Cannon LA, Wenderfer SE, Lewandowski LB, Cooper JC, Goilav B, Knight AM, Hersh AO, Ardoin SP, Sadun RE; CARRA Lupus Nephritis Workgroup. Use of **EuroLupus** Cyclophosphamide Dosing for the Treatment of Lupus Nephritis in Childhood-onset Systemic Lupus Erythematosus in North America. J Rheumatol. 2022 Jun;49(6):607-614.

Malignancy Risk in pSLE

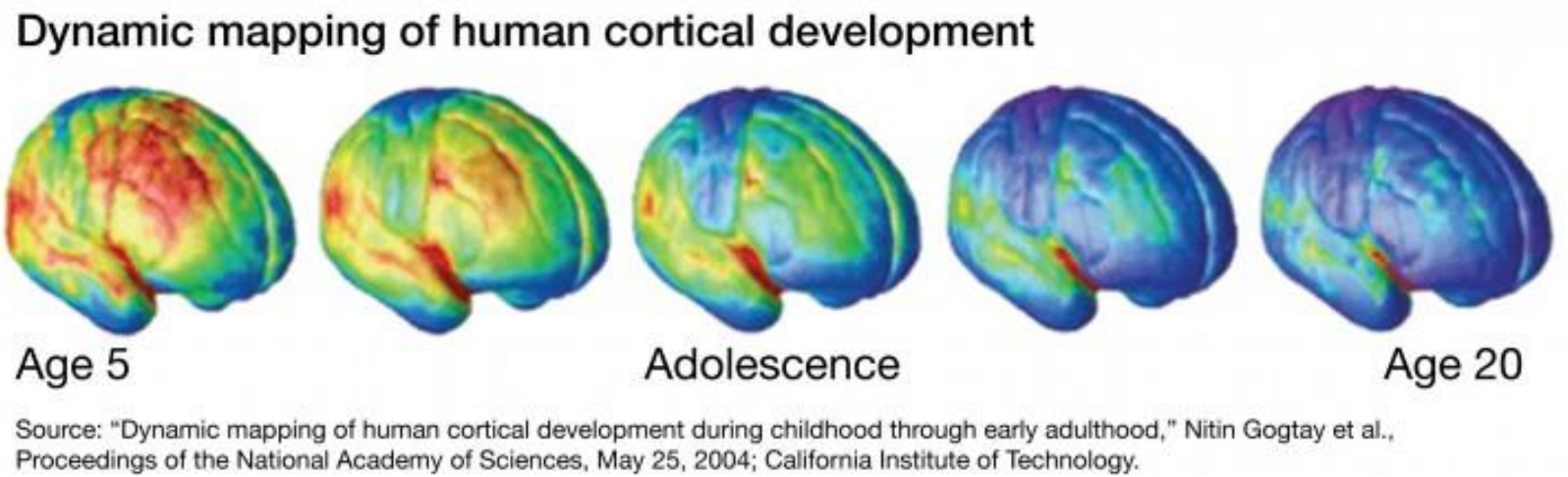
- 12 pSLE registries in North America linked regional cancer registries
  - **~1200 patients** from 1974-2009
  - Mean duration of **follow up: 7.6 years** [IQR 3.4, 10]
  - Standardized incidence ratios
- Higher cancer risk in pSLE population
  - **SIR for all cancers 4.35** (95% CI 2.3-7.4)
  - **NHL** was the most common in the cohort
- Compared to adult SLE studies:
  - NHL with an SIR 4.3, (95% CI 3.5-5.5)
  - **Highest cancer risk in patients < 40 years** →Impact of disease duration and cumulative treatment?

In pediatric lupus, malignancy is uncommon, but risk may be increased relative to the general pediatric population.

Bernatsky et al, Journal of Rheumatology, 2017
Bernatsky et al, J Autoimmun 2013

Neurologic Development

- Gray matter peaks around 10-12 yrs
- Frontal lobes not fully developed until 20's
- Communication between distant brain regions not present until adulthood
- As an example, NPSLE in youth typically occurs during a **critical period brain development**
  - Pre-frontal cortex → complex cognitive function



Source: "Dynamic mapping of human cortical development during childhood through early adulthood," Nitin Gogtay et al., Proceedings of the National Academy of Sciences, May 25, 2004; California Institute of Technology.

Risks & Benefits of Immunosuppression in Pediatric Rheumatic Disease

- **Infection risk** (severe infections have a negative impact)
- Possible **neuro-developmental effects**
- Impact on **growth**
- Increased risk of **malignancy**

- **Control of inflammation** decreases end organ damage & improves outcomes
- Steroid sparing agents decrease **glucocorticoid exposure**

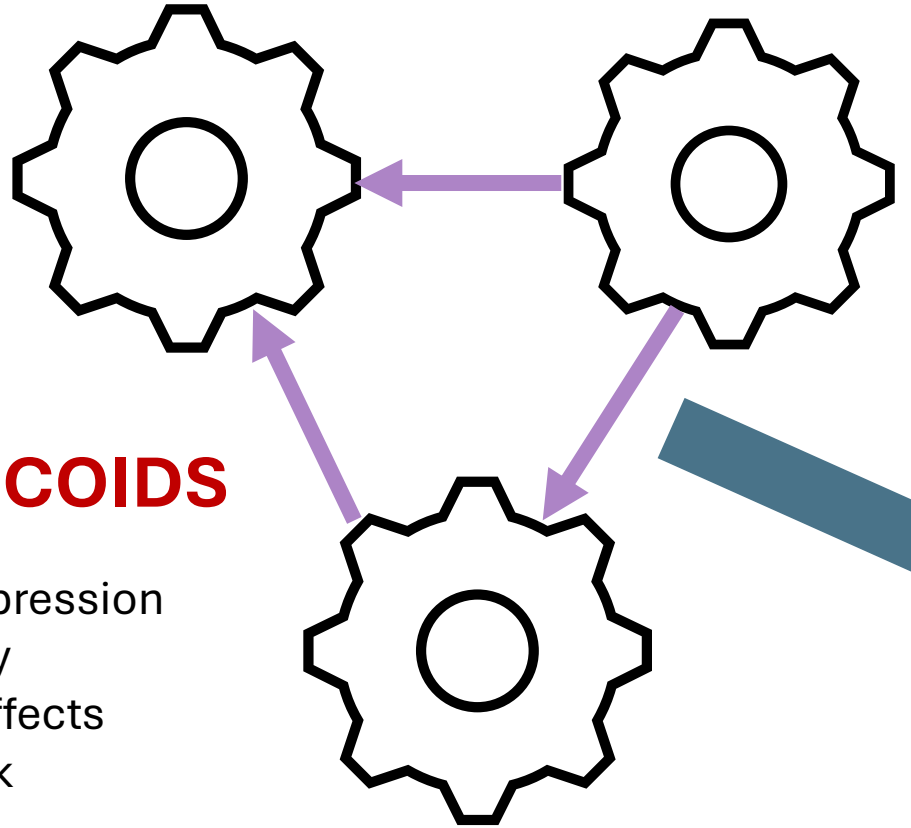
Measuring Outcomes: medications are entangled with disease activity and glucocorticoids

DISEASE ACTIVITY

- Inflammation
- Poor nutrition
- Delayed puberty
- Impaired growth

Non-GC TREATMENT

- Immunomodulation
- Steroid sparing
- Control of inflammation
- Long-term unknowns



GLUCOCORTICOIDS

- Growth suppression
- Bone toxicity
- Metabolic effects
- Infection risk

Net Effect on Growth & Development

What safety data do we have in the short-term & long-term?

Safety and efficacy of intravenous belimumab in children with systemic lupus erythematosus: results from a randomised, placebo-controlled trial

Hermine I Brunner ,[1] Carlos Abud-Mendoza ,[2] Diego O Viola,[3] Inmaculada Calvo Penades,[4] Deborah Levy,[5] Jordi Anton,[6] Julia E Calderon,[7] Vyacheslav G Chasnyk,[8] Manuel A Ferrandiz,[9] Vladimir Keltsev,[10] Maria E Paz Gastanaga,[11] Michael Shishov,[12] Alina Lucica Boteanu,[13] Michael Henrickson,[1] Damon Bass,[14] Kenneth Clark,[15] Anne Hammer,[14] Beulah N Ji,[15] Antonio Nino,[14] David A Roth,[14] Herbert Struemper,[16] Mei-Lun Wang,[14] Alberto Martini,[17] Daniel Lovell ,[1] Nicolino Ruperto ,[18] in collaboration with the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG)

- Safety events were similar between treatment group (79.2%) and placebo group (82.5%)
- Serious adverse events were also similar between groups: LN (2 in each group); infusion reactions were similar as well
- One death in the placebo group

Recent Study Demonstrates Similar Short-Term Efficacy & Safety Between Pediatric and Adult Clinical Trials

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Efficacy and safety of belimumab in paediatric and adult patients with systemic lupus erythematosus: an across-study comparison

Hermine I Brunner ,[1] Carlos Abud-Mendoza ,[2] Masaaki Mori ,[3] Clarissa A Pilkington ,[4] Reema Syed ,[5] Syuji Takei ,[6] Diego O Viola,[7] Richard A Furie ,[8] Sandra Navarra ,[9] Fengchun Zhang ,[10] Damon L Bass ,[11] Gina Eriksson ,[11] Anne E Hammer ,[11] Beulah N Ji ,[12] Mohamed Okily ,[12] David A Roth ,[11] Holly Quasny ,[13] Nicolino Ruperto [14]

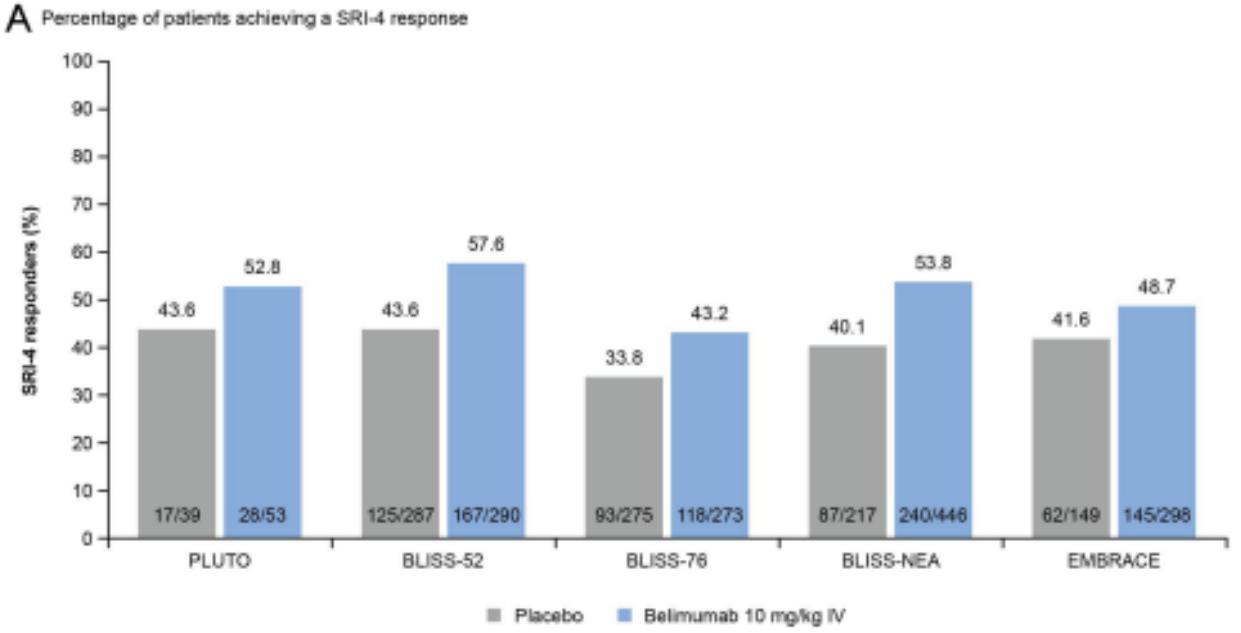


Table 3 Summary of AEs, SAEs and AESIs (mITT or safety population)*

	cSLE study		Pooled aSLE studies	
	Placebo (n=40)	Belimumab 10 mg/kg intravenously (n=53)	Placebo (n=1355)	Belimumab 1, 4 and 10 mg/kg intravenously and 200 mg subcutaneously (n=2815)
Number of patients with ≥1 AE, n (%)				
AE	33 (82.5)	42 (79.2)	1184 (87.4)	2440 (86.7)
Treatment-related AE	15 (37.5)	19 (35.8)	463 (34.2)	1019 (36.2)
SAE	14 (35.0)	9 (17.0)	230 (17.0)	421 (15.0)
AE resulting in study agent discontinuation	5 (12.5)	3 (5.7)	109 (8.0)	184 (6.5)
Death	1 (2.5)	0 (0.0)	6 (0.4)	16 (0.6)

Original Investigation | Pediatrics

Association of Rituximab Use With Adverse Events in Children, Adolescents, and Young Adults

Casey Lee McAtee, MD; Joseph Lubega, MD, MPH; Kristen Underbrink, BS; Kristen Curry, PharmD; Pavlos Msaouel, MD, PhD; Martha Barrow, BS; Eyal Muscal, MD, MS; Timothy Lotze, MD; Poyyapakkam Srivaths, MD; Lisa R. Forbes, MD; Carl Allen, MD, PhD; M. Brooke Bernhardt, PharmD, MS

Rheumatology, 2026, 65(5), keag236
https://doi.org/10.1093/rheumatology/keag236
Published: 26 April 2026
Systematic Review and Meta Analysis

British Society for Rheumatology RHEUMATOLOGY OXFORD

Long-term efficacy and safety of belimumab in children with systemic lupus erythematosus: a meta-analysis of real-world data

Thy Phuong Anh Le[1,2], El-Wui Loh[3,4,5], Ka-Wai Tam[3,6,7,*]

Real-world application of the pediatric Glucocorticoid Toxicity Index in childhood-onset lupus

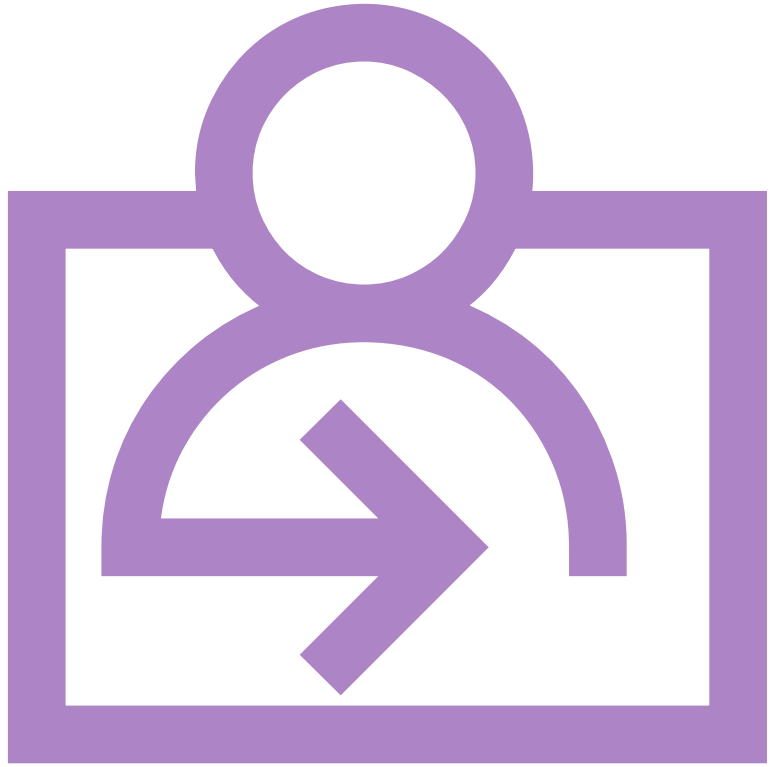
Emily Zhang [a], Sarah Capponi [b], Rebecca Scobell [b], Gabrielle Alonzi [a], Madeline Hlobik [a], Ankana Daga [c], Esra Meidan [a], Holly Wobma [a], Liyoung Kim [a], Lauren A. Henderson [a], Siobhan Case [a,d], Peter A. Nigrovic [a,d], John H. Stone [e], Karen H. Costenbader [d], Mary Beth F. Son [a], Joyce C. Chang [a,b,*]

Do we have what we need?

- **Short term safety** likely similar to adults and adult data could be leveraged
- Patients and families want to know about **long term safety** events (**e.g. final height attainment, serious infections, infertility, malignancy**) where there is:
  - Confounding by disease severity
  - Treatment with multiple medications
  - These are RARE events
  - Unknown risk window

What is Needed for Long Term Safety Data Collection?

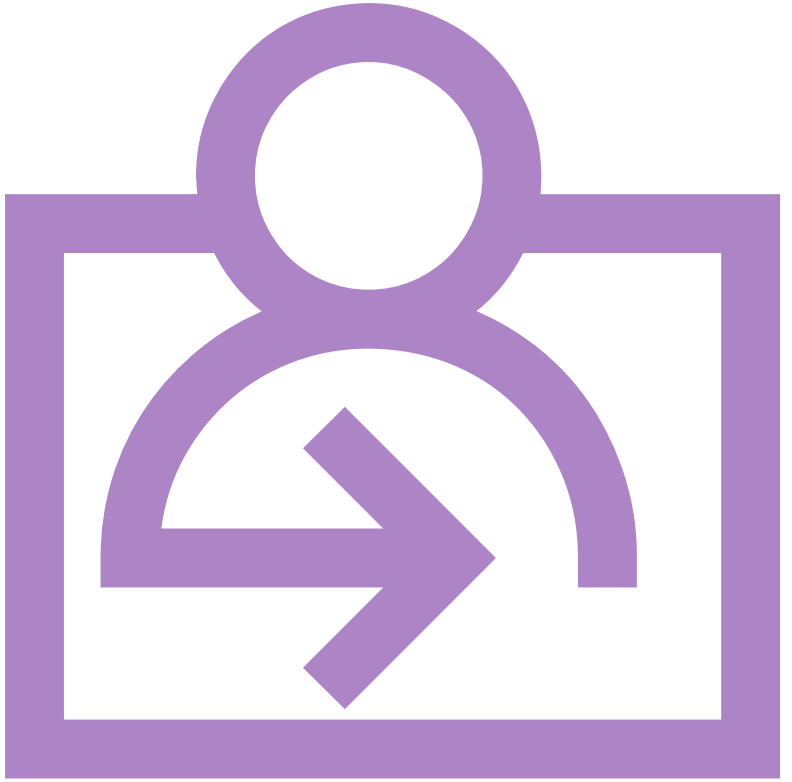
- Systematic collection – missing data might occur in the highest risk groups
- Long term collection – need longitudinal data to identify signals for rare outcomes
- Multiple outcomes of interest
- Ability to track medication combinations over time



Many of these features are age-independent and important in adult lupus populations as well – important to synergize where possible

What might make pediatric populations different?

- Higher glucocorticoid burden because of *lack of approved medications*
- Higher genetic burden
- Higher malignancy risk
- Longer follow up period required



Possible Solutions

- Phase IV studies
- Registries with medication & long term follow up data
- Linkages with/across administrative databases
- Registration for all pSLE trial participants in long term studies

SAFETY EVENTS

- All Serious Adverse Events reported
- All Events of Special Interest reported (e.g., uveitis, optic neuritis, tuberculosis)
- Standard SAE form for all events: description, recent medications, diagnostic studies, event treatment, outcome
- MedDRA codes assigned centrally by clinical coding specialists
- CTCAE Grade collected for all events
- Ability to obtain additional documentation (e.g., pathology reports)

LONG-TERM FOLLOW-UP

- Collect data for at least 10 years per participant
- Participants who leave CARRA Registry site (e.g., relocation, age out of care, disease remission) are transitioned to long-term follow-up program
- Collect patient-reported data about medication use, disease activity, PROs, and safety events
- Permits evaluation of adulthood outcomes of childhood-onset disease and treat

CARRA REGISTRY

Summary

- There are reassuring data for short term safety outcomes
- Long term safety outcomes are rare so we need to study as many children as possible for as long as possible
- Collaboration amongst all stakeholders is needed to optimize this kind of data collection