膠原病 Journal Club　　2023/2/21 住友

Belimumab use during pregnancy: a summary of birth defects and pregnancy loss from belimumab clinical trials, a pregnancy registry and postmarketing reports

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背景と目的

- SLE女性の妊娠では, 先天異常のリスク, 流産リスクが高い.
  - 非SLE女性より流産率 4%高い (Pediatr Rheumatol Online J 2018;16:26.)
- 原因として, 疾患活動性, 抗リン脂質抗体, SLEの治療薬 (CY, MMF, LEF, MTX) が考えられる.
- 臨床試験で妊婦は除かれるため, Belimumabのデータは限られる.
- サルのBelimumab経静脈投与実験では胎児や流産への影響は認めなかったが, 出生サルのB細胞は減少し, 3Mで回復した (GSK資料).
- Belimumab投与中のSLE妊娠の先天異常, 流産を調査した.

方法

- 観察研究（今までで最大規模）
- Belimumabの18臨床試験, 妊娠レジストリー (Belimumab Pregnancy Registry; BPR), 市販後/自発的な報告 (2020/3/8まで).
- Belimumab曝露時期, 併用薬剤, 潜在的な交絡因子を記述的に要約した.

妊娠，出産，先天異常，流産/死産 のまとめ

Table 1 Summary of pregnancies, birth defects and pregnancy loss recorded in clinical trials, the BPR and postmarketing/spontaneous reports to 8 March 2020 **市販後調査**

Outcomes	Clinical trials* 臨床試験		BPR 妊娠レジストリー		Postmarketing/spontaneous reports
	Belimumab+ST	Placebo+ST	Belimumab+ST, prospective cohort†	Belimumab+ST, retrospective cohort‡	Belimumab+ST
Total number of pregnancies, N	181§	28	57	10	310
Lost to follow-up/unknown, n	13	3	4	0	140
Ongoing, n	1	0	5	0	27
Known outcome, n	167	25	48	10	143
Pregnancies with known outcomes excluding elective terminations, N	110¶	16	48	8	137¶
Pregnancy loss, n (%)	35/110 (31.8)	7/16 (43.8)	2/48 (4.2) (95% CI 0.0% to 9.8%)**	4/8 (50.0)	43/137 (31.4)
Miscarriage with no apparent birth defect, n††	33	5	2	4	40
Miscarriage with birth defect, n†† 流産<20w	0	1	0	0	1
Stillbirth with no apparent birth defect, n‡‡	2	1	0	0	1
Stillbirth with birth defect, n‡‡ 死産≧20w	0	0	0	0	1
Total number of pregnancies ending in live births, N§§	72	9	46	4	92
Pregnancies with live infant with birth defect, n (%) 先天異常	4/72 (5.6)	0/9	10/46 (21.7) (95% CI 9.8% to 33.7%)**	0/4	1/92 (1.1)
Pregnancies with live infant with no apparent birth defect, n	68	9	36	4	91

*Post hoc summary of double-blind (completed) and open-label (completed/ongoing) phases of clinical studies and NCT03312907, where all arms include belimumab treatment. The following clinical trials were included: NCT01345253, NCT01649765, NCT01597622, NCT01705977, NCT01632241, NCT01894360, NCT03312907, NCT04136145, NCT00410384, NCT00424476, NCT00724867, NCT00732940, NCT00712933, NCT01484496, NCT01597492, NCT00071487, NCT01639339 and NCT00583362.

†Women who enrolled in the registry before the end of pregnancy regardless of known normal or abnormal prenatal test results.

‡Pregnancy ended before enrolment or at the time of first contact with the registry.

§Includes two pregnancies in healthy volunteers (one lost to follow-up and one ended in elective termination).

¶Ectopic and molar pregnancies are included (three in the clinical trials and two in the postmarketing/spontaneous reports); those were not considered pregnancy losses.

**95% CIs were calculated in PASS 2022 V.22.0.2 (ncss.com/software/pass) by ad hoc analysis based on the Wald method (simple asymptotic) without continuity correction.

††Defined as pregnancy loss before the 22nd week of pregnancy; however, this can vary by region and data source. The BPR defines pregnancy loss occurring <20 weeks as miscarriage.

‡‡Defined as pregnancy loss from/after the 22nd week of pregnancy onwards; however, this can vary by region and data source. The BPR defines pregnancy loss ≥20 weeks as stillbirth.

§§There were four twin pregnancies (two BPR and two postmarketing) all ending in live births. Birth defect was diagnosed in one (BPR) of these eight infants. Outcomes reported are per pregnancy and not per infant.

BPR, Belimumab Pregnancy Registry; ST, standard therapy.

結果：先天異常

- 319 妊娠 (選択的中絶を除く) のうち, 223人が出生.
- 18臨床試験： Belimumab 曝露妊娠で 4/72 (5.6%)
  Placebo 妊娠で 0/9 で先天異常を確認.
- BPR： 前向きcohort (妊娠結果前登録) のBEL曝露妊娠で10/46 (21.7%)
  後ろ向きcohort (妊娠結果後登録) のBEL 曝露妊娠で 0/4
- 市販後/自発的な報告： Belimumab 曝露妊娠で1/92 (1.1%)
- データセット全体で先天異常の一貫したパターンはなかった.

Table 2 Cases of birth defects in patients receiving belimumab in clinical trials, the BPR and postmarketing/spontaneous reports

Cumulative count of reported cases	Reported defect	The event fulfils MACDP* criteria?	EUROCAT classified defect?†		Additional considerations
Clinical trials‡	臨床試験				
1	Microcephaly	NP	NP	小頭症	–
	Atrioventricular septal defect	NP	NP	ASD	There is no reason to predict an IgG antibody would affect interventricular septum development (which completes by 7 weeks in humans) because belimumab is highly specific for B-lymphocyte stimulator which binds to receptors primarily localised to B lymphocytes and because there is very little placental transfer of IgG antibodies during the first trimester.[55]
	Unbalanced translocation, involving chromosomes 11 and 13	NP	NP	11:13転座	Unbalanced translocation involving chromosomes 11/13 is not plausibly linked to belimumab because it is not expected that a monoclonal IgG antibody would interact with DNA or chromosomal material
2	Bilateral enlarged kidneys with severely abnormal function	NP	NP	腎腫大・機能異常	Oligohydramnios, ambrisentan use
	Positional deformities of the head and extremities	NP	NP		–
3	Dandy-Walker syndrome	NP	NP		–
4	Mild pulmonic stenosis (valvular with no intra-atrial shunt)	NP	NP	軽度のPS	–
BPR	妊娠レジストリー				
1	Bilateral clubfoot	Yes	Yes	内反尖足	Can occur due to mechanical factors that take place within the pregnancy
2	Non-descending testis	Yes	No	停留睾丸	May not have involved belimumab exposure during the critical window of development
3	Very mild Ebstein's anomaly of the tricuspid	Yes	Yes		–
4	Congenital heart block	Yes	No	心ブロック	Confounded by neonatal lupus with presence of anti-Ro/SSA and anti-La/SSB antibodies
5	Small ventricular septal defect	Yes	Yes	小さいVSD	Described as tiny atypical ventricular septal defect and muscular
	Congenital hydronephrosis	Yes	Yes	水頭症	–
6	Low-lying conus medullaris	Yes	Yes		–
	Pelviectasis	Yes	No		–
7	Positional plagiocephaly	Yes	No		Can occur due to mechanical factors that take place within the pregnancy
	Positional torticollis	Yes	No	斜頸	Can occur due to mechanical factors that take place within the pregnancy
8	Small fenestrated atrial septal defect	ED§	Yes		Prenatal testing prior to enrolment with abnormal results
9	Severe Arnold-Chiari type II malformation	Yes	Yes		Enrolled in third trimester, prenatal testing done prior to enrolment but results unknown
10	Ankyloglossia	Yes	No	舌小帯短縮症	
Postmarketing/spontaneous reports	市販後調査				
1	Extrarenal pelvis	NP	NP		Sibling with a cardiac defect reported separately and included in this report; this presents a potential for a reporting bias and/or an underlying genetic predisposition

BEL投与患者の児の先天異常

- Clinical trial：
  Belimumab群の4例中3例はBELと無関係と評価.
  Placebo群で先天異常なし.

- BPR：
  50妊娠中10例で先天異常.
  重症度や臓器障害は多様.

結果：流産/死産 (選択的中絶を除く)

- 18臨床試験：Belimumab 曝露女性の 31.8% (35/110), Placebo 曝露女性の 43.8% (7/16) で発生.
- BPR：前向きコホートの 4.2% (2/48), 後ろ向きコホートの50% (4/8)で発生.
- 市販後/自発的な報告：31.4% (43/137) で発生.
- 臨床試験, BPR でBelimumabに曝露されたすべての女性は併用薬を投与され, 交絡因子 and/or 欠損データあり.

Table 3 Patient characteristics and concomitant medications of interest from belimumab clinical trials (post hoc summary) and the BPR (ad hoc summary)

	Birth defects	Pregnancy loss	
	Belimumab	Belimumab	Placebo
Clinical trials* 臨床試験	n=4	n=35	n=7
Mean (SD) age at enrolment (years)	27.5 (4.51)	28.6 (5.29)†	32.0 (5.48)
Mean SLEDAI at baseline (SD)	11.0 (7.75)	9.2 (4.80)‡	8.4 (1.81)
Trimesters of exposure, n (%)			
First trimester only	1 (25)	27 (77)	3 (43)
First and second trimesters	3 (75)	7 (20)	4 (57)
First, second and third trimesters	0	1 (3)	0
Prednisone use >10 mg/day, n (%)	–	12 (34)	2 (29)
Concomitant medications of interest, n (%)			
Azathioprine	0	6 (17)	2 (29)
Enalapril	0	4 (11)	0
Hydroxychloroquine	4 (100)	18 (51)	2 (29)
Lisinopril	0	2 (6)	0
Losartan	0	3 (9)	0
Methotrexate	0	2 (6)	0
Methylprednisolone	0	4 (11)	0
Mycophenolate	0	4 (11)	0
Corticosteroids: Prednisone/meprednisone/prednisolone	4 (100)	21 (60)	3 (43)
Tretinoin	0	1 (3)	0
aCL baseline status, n (%)			
Baseline status data available		13	6
aCL status positive at baseline		5 (39)	0
BPR 妊娠レジストリー	n=10	n=6	–
Mean (SD) age at enrolment (years)	34.2 (3.2)	34.0 (3.4)	–
Earliest belimumab exposure, n (%)			
Preconception	9 (90)	5 (84)	–
First trimester only	1 (10)	1 (17)	–
Last belimumab exposure, n (%)			
First trimester	2 (20)	0	–
Second trimester	6 (60)	0	–
Postpartum	2 (20)	6 (100)	–
Concomitant medications of interest, n (%)			
Antimalarials	9 (90)	3 (50)	–
Immunosuppressants			
Azathioprine	2 (20)	0	–
Cyclosporin	1 (10)	1 (17)	–
Methotrexate	1 (10)	1 (17)	–
MMF	0	1 (17)	–
Corticosteroids	6 (60)	3 (50)	–
Epilepsy medication	1 (10)	0	–
NSAIDs	2 (20)	1 (17)	–
Folate	7 (70)	2 (33)	–
ACE inhibitors	0	0	–
Heparin	2 (20)	0	–
Aspirin	3 (30)	1 (17)	–
Calcium channel blockers	0	1 (17)	–
Beta blockers	0	1 (17)	–

*Other concomitant medications in the birth defects group include, but are not limited to, prochlorperazine, zolpidem, amlodipine, furosemide and ambrisentan (all n=1). Relevant concomitant medications were teratogens, medications associated with pregnancy loss, medications indicating severe or refractory diagnosis or acetylsalicylic acid/warfarin.
†N=34.
‡N=33.
aCL, anticardiolipin; BPR, Belimumab Pregnancy Registry; MMF, mycophenolate mofetil; NSAID, non-steroidal anti-inflammatory drug.

母体の情報

- Clinical trial: 先天異常4例の併用薬はCS/HCQ投与.
- 流産/死産例は, BEL群(35例)中27人が1st trimesterにのみ曝露され, 同時期に流産した. 併用薬はCS/HCQ/ AZAが最も多い.
- 22人は代替診断が, 8人は併用薬が関連すると判断されている.

- BRR：流産の6名に妊娠糖尿病やHELLPはいなかった.

Discussion：先天異常

- BELに関連した先天異常のリスクの判断ができていない.
  - 添付文書上は有益性が上回るときのみ推奨
  - EULAR/BSR：妊娠中の投与は注意を推奨
  - ACR：妊娠判明した時点で中止を推奨
- これらは妊娠関連のデータ不足が理由.

- 台湾13妊娠 (BEL曝露) 11出生で先天異常なし
- イタリア12妊娠 (BEL曝露) 11出生で先天異常なし

Discussion：流産/死産

- BEL 曝露女性の 31.8% (35/110), Placebo曝露女性の 43.8% (7/16) で発生した.
- 既報では, BEL曝露女性の29.5% (13/44) , Placeboの50% (4/8)で発生 (Lupus 2013;22:144–54, 今回のデータに含まれる).

問題点

- Belimumabに曝露された妊娠の数が少ない
- 交絡因子の存在
- 完全な情報把握が困難（SLEDAI, SS-A, APL, 併用薬剤）
- データ源の不均一性
- 臨床試験, 市販後/自発的調査が, 妊娠アウトカム調査目的にデザインされていない
- BPRに自分で登録する患者の選択バイアス
- このため, Belimumab使用による先天異常と流産/死産のリスクに関する推奨の作成が困難である.

結論

- Belimumabに曝露された妊娠の先天異常と流産/死産について, 複数のデータ源からの情報を要約した.
- データの限界を考慮して, 記述的な提示をすることしかできなかった.
- 妊娠研究への患者登録率が増加し, 妊娠研究におけるデータ収集の質が向上することが, 薬剤曝露後の先天異常と流産/死産リスクの適切な評価が必要.