Pregnancy appears difficult to obtain and TNF-α blockers cannot always be discontinued in women with rheumatic diseases

Sirs,

Tumour necrosis factor α (TNF-α) blockers are often used in women of childbearing age (1, 2). The objective of this study was to describe the outcomes of pregnancy wish in women treated with TNF-α blockers for rheumatic diseases and to assess the feasibility of recommended TNF-α blockers interruption before pregnancy.

We conducted a systematic retrospective study of medical records of one tertiary rheumatology unit, for all women who had either been considering a pregnancy or who were pregnant while receiving or after having received TNF-α blockers between 1998 and 2006. Pregnancies were considered "exposed" to TNF-α blockers at the time of conception, if conception occurred before 5 half-lives of TNF-α blocker discontinuation: 24 days for etanercept, 50 days for infliximab, and 70 days for adalimumab.

Twenty patients representing 23 pregnancy wishes were analysed: 13 had rheumatoid arthritis and 7 spondyloarthritis (Table I). Of 20 women with a pregnancy wish, 7 (35%) failed to conceive with a median follow-up of 15.3 months; median delay before pregnancy was 10.8 months (range 0-29). A flare of rheumatic disease occurred in 35% of pregnancy wishes. Recommended discontinuation of TNF-α blockers before conception was not possible in 12/23 cases (52%): no initial discontinuation in 9 cases and reintroduction after initial discontinuation in 3 cases. Fourteen pregnancies were exposed to TNF-α blockers at the time of conception: median exposure time was 19 days after conception (range 40 days before-90 days after), 8 were exposed to etanercept, 4 to adalimumab, and 2 to infliximab. Their outcomes were as expected in the general population: 9 live births (64%), 3 miscarriages (21%), 2 therapeutic terminations (14%) (co-medication with methotrexate). No foetal or neonatal malformation and no pre-term delivery were reported among the total number of 21 pregnancies.

In this study, the interruption of TNF-α blockers was not possible for 12/23 pregnancy wishes (52%) for two main reasons: the activity and severity of the rheumatic disease and a long time to conception (10.8 months). In addition we reported that 35% of women with a pregnancy wish had not conceived after a median follow-up of 15.3 months and we noted the recourse to procreation assistance techniques or ovarian stimulation in 5 of 20 women with a pregnancy wish. This is in keeping with other studies which report a longer time from first attempting conception to pregnancy in rheumatic diseases (3, 4). We cannot know if this reduced fecundity is due to the severity and activity of the rheumatic disease or the treatment with TNF-α blockers and the time to conception.

Regarding outcomes of pregnancy, our reassuring results are consistent with published series (5-7). However, congenital anomalies that are part of the VACTERL spectrum have been recently reported (8).

In conclusion, compliance to recommendations for discontinuation of TNF-α blockers before conception is difficult in daily practice, because of conception difficulties and rheumatic flares for women with rheumatic diseases. Despite the small sample size of this study, no signal of increased teratogenicity was detected for pregnancies exposed to TNF-α blockers. Further studies with prospective follow-up of pregnancies and long-term follow-up of children are necessary.

Table I. Characteristics of women receiving TNF-α blockers for rheumatic diseases between 1998 and 2006 and reporting a pregnancy wish in one centre.

	Pregnancy wish = 23 (n. women = 20)		
	Total	With pregnancy	Without pregnancy
Number of women	20	13	7
Number of pregnancies	16	16	0
Median age, yrs (min; max)	32.6 (23.0; 39.3)	32.3 (23.0; 39.3)	34.9 (27.6; 35.7)
Underlying diagnosis			
Rheumatoid arthritis	13	8	5
Spondyloarthritis	4	3	1
Psoriatic arthritis	3	2	1
Juvenile arthritis	0	0	0
Median disease duration, yrs (min; max)	6.9 (1.8; 33.3)	6.2 (1.8; 15.2)	9.9 (4.7; 33.3)
n. previous DMARDs median n. (min; max)	4 (0; 6)	4 (0; 5)	3 (1; 6)
Etanercept, n.	15	11	4
Infliximab, n.	5	3	2
Adalimumab, n.	3	2	1
Median n. of previous children (min; max)	1.0 (0; 2)	1.0 (0; 2)	0.5 (0; 1)

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Competing interests: none declared.

References

1. MCLEOD C, BAGUST A, BOLAND A *et al*.: Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systemic review and economic evaluation. *Health Technol Assess* 2007; 11: 1-158.
2. GARTLEHNER G, HANSEN RA, JONAS B, THIEDA P, LOHR KN: The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: A systematic review and metaanalysis. *J Rheumatol* 2006; 33: 2398-408.
3. OESTENSEN M: New insights into sexual functioning and fertility in rheumatic disease. *Best Pract Res Clin Rheumatol* 2004; 18: 219-32.
4. FAUTREL B, BENHAMOU M: Rhumatisme inflammatoire chronique et procréation. *Gynecol Obstet Fertil* 2007; 35: 848-52.
5. KATZ JA, ANTONI C, KEENAN GF, SMITH DE, JACOBS SJ, LICHTENSTEIN GR: Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004; 99: 2385-92.
6. HYRICH KL, WATSON KD, DIXON WG, SILMAN AJ, SYMMONS DPM: Pregnancy experience in women with rheumatic diseases exposed to biologic agents: results from the BSR biology register. *Arthritis Rheum* 2006; 54: 2701-2.
7. CHAMBERS CD, JOHNSON DL, JONES KL: Pregnancy outcome in women exposed to anti-TNF alpha medications: The OTIS rheumatoid arthritis in Pregnancy Study. *Arthritis Rheum* 2004; 50: S479.
8. CARTER JD, LADHANI A, RICCA LR, VALERIANO J, VASEY FB: A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. *J Rheumatol* 2009; 36: 635-41.