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Intentional etanercept use during pregnancy for maintenance of remission in rheumatoid arthritis

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ABSTRACT

Objectives. *Rheumatoid arthritis is associated with an increased risk of adverse pregnancy outcomes. TNF inhibitors are effective in the treatment of signs and symptoms of the disease although their safety during pregnancy is debated.*

Methods. *Two cases of women with rheumatoid arthritis in complete remission of the disease with etanercept who decided to continue the therapy throughout their pregnancy are presented. A longitudinal evaluation of the disease activity showed a satisfactory control and good pregnancy outcomes were obtained. A flare of the disease after delivery was not observed.*

Conclusions. *Etanercept seems to be safe during pregnancy and lactation. Good control of the activity of the disease was reported throughout the pregnancy and during puerperium, when a reactivation of rheumatoid arthritis is often observed.*

Introduction

Rheumatoid arthritis (RA) is an inflammatory disease that presents with a wide array of clinical and instrumental (laboratory and radiological) features (1). Its clinical onset and subsequent progression may follow several different patterns that are usually slow, but may occasionally be rapidly progressive. Pregnancy has been reported to improve signs and symptoms of RA up to a complete remission, followed by deterioration postpartum (2, 3). The mechanisms that underlie this phenomenon are not completely understood (4). On the other hand, women with RA present an increased risk of adverse pregnancy outcomes (5).

Still, the exact pathogenetic mechanisms of RA are not fully defined, although an immune-mediated syndrome with the involvement of both the innate and the adaptive branches of the immune system has been demonstrated. Pro-inflammatory monokines, such as TNF-α, IL-6 and IL-1β, seem to play a pivotal role in promoting bone destruction and loss of cartilage (6). TNF-α sustains a local and systemic inflammation by inducing the production of IL-6 and IL-1, by enhancing the expression of cell-surface adhesion molecules on endothelial and other cells and by activating different cell populations. Pregnancy itself is associated with a systemic inflammatory activation with several cytokines involved (7, 8).

TNF inhibitors have been shown to be effective in the treatment of signs and symptoms of RA although an evidence-based consensus on the safety of this therapy during pregnancy is still unavailable (9). Discontinuing the therapy early in pregnancy is often suggested so as not to increase the risk of embryotoxicity, teratogenicity or pregnancy loss, although the overall incidence of adverse events in pregnant women on TNF inhibitors is within the range of the general population (10).

Limited data are available regarding the use of etanercept during pregnancy and lactation (11, 12). Sporadic case reports of single uneventful pregnancies have been published so adding very little to general knowledge on the safety of these drugs. A single series has been reported by Berthelot *et al*. (13) who described 12 women treated with TNF inhibitors during pregnancy. Although, the series was heterogeneous for indication (spondylarthropathies, rheumatoid arthritis, juvenile idiopathic arthritis, and psoriatic arthritis) and duration of therapy (only two cases till delivery), no significant adverse outcomes were reported. A single case of severe malformation has been reported as associated with etanercept use during pregnancy, namely a VACTERL syndrome (a multiorgan malformation) (14). Still, it is rare disease with different clinical manifestations that makes difficult to identify that association as univocally causative (15).

Case report.

Here we report two cases of young women (23 and 28 years old) with RA longing for pregnancy who obtained a complete remission of the disease with etanercept after several attempts with traditional DMARDs and decided to continue the therapy throughout their pregnancy. An informed consent was signed before conception where the limited data available about that drug during pregnancy were clearly stated

with the approval of the local ethics committee. After a few months, a pregnancy was obtained spontaneously and closely monitored by the rheumatologist and the gynaecologist. RA activity was monitored using the disease activity score (DAS) 28 with C-reactive protein dosage without GH as this was reported to be the best tool for calculating disease activity during pregnancy (16). The values of 3.2 and 2.6 are usually considered as low disease activity and remission thresholds, respectively. Before pregnancy the DAS28(3)-CRP in patient 1 and 2 was 1.6 and 2.1, respectively, and was assessed every three months throughout the pregnancy and in puerperium. No other drugs were associated to etanercept (glucocorticoids, FANS or other DMARDs) during pregnancy and lactation but paracetamol when necessary. Both pregnancies were uneventful with a normal fetal growth and without clinical signs of reactivation of the disease. Steady values of DAS-28(3)-CRP with a slightly raise in the curve during pregnancy were observed (Fig. 1), although they were well below the 3.2 threshold. The expected reactivation of the disease after delivery (2, 3) was not observed up to 9 months of follow up. Paediatric evaluation of newborns was within the limits at birth and clinical follow-up of the infants up to 9 months of age was satisfactory as for weight, physical and neurological development.

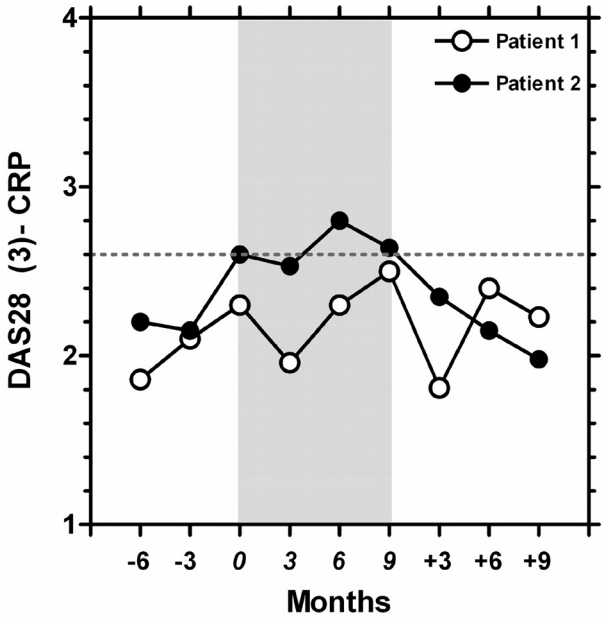

Fig. 1. Longitudinal evaluation of DAS28(3)-CRP values before conception, during pregnancy (within the grey gap) and after delivery. The dotted line represents remission threshold (2.6).

Discussion.

Although based on limited data, etanercept seems to be safe during pregnancy and lactation and the two cases here reported represent a further support to previous articles. Indeed, it has to be considered that the two patients were both young and healthy apart from RA. RA presented more than 5 years before the reported pregnancy reaching a severe degree of the activity (DAS-28 higher than 6 points) in both cases with poor response to other medications. We may argue that perinatal complications (miscarriage, preterm birth, neo-natal jaundice, low birth weight, …) reported by other Authors (17, 18) could be linked to the pre-pregnancy general conditions of the patients more than the medication itself.

The general adaptation of the immune system during pregnancy towards foetal/paternal antigens are thought to be responsible for the ameliorating effect of pregnancy on RA whereas the flare after delivery is often explained by a gradual returning of the immune system to a prepregnancy state after delivery. Given the findings of this study, we hypothesize a possible role of a discontinue therapy early in pregnancy on the reactivation of the disease. In fact the results obtained before pregnancy on RA control using etanercept in these two patients were consistently observed after delivery without a flare in puerperium. On the other hand, the improvement of RA symptoms induced by the pregnancy may well support the decision to discontinue the therapy as suggested by some Authors (15, 18) whenever possible (9).

The strength of this report is based on the intentional use of etanercept only with a close monitoring of both pregnancy and RA activity. To the best of our knowledge, this is the first longitudinal description of the activity of AR during pregnancy using etanercept only to maintain the remission of the disease. This may represent the basis for planning a multicentre prospective study to validate the safety of etanercept during pregnancy.

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