Arthritis in pregnancy: the role and safety of biological agents

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Summary: As the average age of mothers is increasing there is a greater likelihood that they will have intercurrent medical problems at the time of their pregnancy. As a group, autoimmune diseases are relatively common with an estimated population prevalence of 5–8%. At least 75% of autoimmune diseases occur in women, most frequently during the child-bearing years. Rheumatoid arthritis (RA) is the most common chronic inflammatory disease of joints and occurs in approximately 1% of the population with women being affected two or three times more than men and many of the women being of child-bearing age. The pathogenesis of RA is multifactorial with a role for T-lymphocytes, B-lymphocytes, macrophages and other pro-inflammatory cells producing a plethora of cytokines including interleukin-1 and tumour necrosis factor- α in the synovial cavity resulting in irreversible damage to cartilage, soft tissues and bone.¹ The drug treatment of RA involves the use of disease-modifying agents to reduce or prevent permanent tissue damage. There is a new class of drugs that can be used to target specific cells and cytokines that have been called 'biological agents'. These drugs have been shown to significantly reduce inflammation and to retard the progression of joint damage in RA thereby reducing symptoms and improving function.²

Keywords: clinical pharmacology, drugs (medication), immunology, rheumatology

INTRODUCTION

The biological disease-modifying antirheumatic agents or 'biologics' available for use in Australia for inflammatory musculoskeletal disorders include agents that inhibit tumour necrosis factor - α (TNF- α), namely adalimumab (Humira), etanercept (Enbrel) and infliximab (Remicade), the interleukin-1 (IL-1) receptor antagonist anakinra (Kineret), the CTLA4 analogue abatacept (Orencia) and rituximab (Mabthera), which is a monoclonal antibody to CD20 and which reduces B-cell numbers. These agents are being increasingly used to treat a variety of conditions including rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis as well as non-rheumatic autoimmune diseases such as Crohn's disease and psoriasis. The efficacy of these medications in RA is improved when used in combination with other disease-modifying drugs, particularly methotrexate. In Australia, the Pharmaceutical Benefits Scheme will only support the use of infliximab, anakinra and rituximab for RA in patients taking methotrexate. Therefore, patients are often on a combination of traditional disease-modifying drugs and biologics.

A questionnaire was sent to 600 members of the American College of Rheumatology regarding their perception of fetal risk and the use of birth control for women using disease-modifying antirheumatic drugs, which included infliximab and etanercept as well as leflunomide and methotrexate. Of the 175 respondents, 38.6% and 46.5% agreed that pregnancy was contraindicated in women taking etanercept or infliximab, respectively, compared with 95% and 92.5% for methotrexate and leflunomide, respectively. Accordingly they recommended

birth control in 75% of women taking etanercept and 73.4% of women taking infliximab (compared with over 95% for leflunomide and methotrexate). Two pregnancies were exposed to infliximab and 15 to etanercept, including one who was also exposed to methotrexate. There were no anomalies reported in the babies exposed to infliximab or etanercept.³

It is important to note that much of the data with regard to exposures to these medications is difficult to interpret for a number of reasons: the actual number of exposed pregnancies is small; the women have often severe underlying medical conditions that in and of themselves may contribute to poor pregnancy outcomes; many of the women take multiple medications some of which are known teratogens, such as methotrexate; and the ascertainment and timing of the exposures is often problematic (for example pregnancies notified retrospectively to drug companies may be biased towards adverse outcomes and exact timing of the exposure in relation to gestation is often inaccurate). Given that all these agents are new and that relatively few women take these medications during pregnancy, there is extremely limited data available about their safety in human pregnancy with regard to infant outcome and risks of major birth defects as well as other adverse pregnancy outcomes. Even less is known about potential long-term sequelae (if any) of these agents such as effects on growth or on the developing immune system.

Due to the paucity of data available about the safety of this group of drugs in human pregnancy, the Organization of Teratology Information Specialists (OTIS) established an Autoimmune Diseases in Pregnancy Project to study not only the course of autoimmune diseases during pregnancy, but also the effects of the biological agents (predominantly adalimumab) on pregnancy and infant outcome.⁴

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Other registries have also been established to address questions regarding the safety of these agents in pregnancy. In the United Kingdom, all patients commenced on a biologic for arthritis must be entered onto the British Society for Rheumatology Biologics Register. As of August 2005, there were 11,473 patients on the register of whom 91% had RA. There were 35 pregnancies with outcome information available on 32 patients. Twenty-three patients were exposed at the time of conception (etanercept 17, infliximab 3 and adalimumab 3). All but two discontinued in the first trimester. One continued etanercept until 20 weeks and one throughout pregnancy. There were six first trimester miscarriages, four taking etanercept, one taking infliximab and one on adalimumab. Methotrexate was being used as concomitant therapy in three of these patients. Elective first trimester terminations were performed on three patients and there were 13 live births, one of whom was four weeks premature (etanercept and leflunomide), one low birth weight 2180 g (etanercept) and one woman who had recurrent cystitis on adalimumab and methotrexate and who had a normal birth. There were no congenital malformations.⁵

Although anti-TNF antibodies are species specific, it is important to note that animal studies with soluble TNF receptor/IgG heavy chain chimeric proteins and monoclonal antibodies report no maternal or embryofetal toxicity and no teratogenicity. In addition, the molecular structures of infliximab, etanercept and adalimumab mean that they are unlikely to cross the placenta in the first trimester, although placental transfer may occur later in pregnancy. One concern about the use of these agents at any stage during pregnancy is potential maternal toxicity with risks of both morbidity and even mortality in women with severe congestive cardiac failure, as well as the risks of severe infection. There are also theoretical concerns that TNF- α antagonists could interfere with ovulation and implantation but these have not been borne out in clinical practice.⁶

INFLIXIMAB

Infliximab is a chimeric monoclonal IgG antibody to human TNF- α and is used to treat RA as well as severe Crohn's disease. Infliximab neutralizes the biological activity of TNF- α by binding to both the soluble and membrane-bound protein. Because infliximab does not cross-react with TNF- α in species other than humans and chimpanzees, relevant animal reproductive toxicology studies have not been performed. However, reproductive studies with an analogous mouse antibody showed no evidence of teratogenicity or of maternal or embryo toxicity. Because the antibody has a large molecular weight it is not clear whether it crosses the placenta (passage of large doses of intravenous gammaglobulin from mother to fetus have been documented, particularly in the latter part of the third trimester). Because the drug has a long elimination half-life (between 8 and 9.5 days) inadvertent exposures during early pregnancy are likely to occur.

One theoretical concern regarding the possible teratogenicity of infliximab is the fact that thalidomide, a major recognized teratogen, is a potent inhibitor of TNF- α production. Although the precise mechanism for thalidomide's teratogenicity is unclear, it affects TNF- α production by accelerating the degradation of the messenger RNA that codes for the protein, whereas infliximab acts as both a cytokine carrier and as a

TNF antagonist, resulting in the TNF being rendered biologically inactive.

The first large series of pregnancy outcomes in women exposed to infliximab was published by Katz *et al.* in 2004 and included pregnancies ascertained by the infliximab safety database in women being treated for Crohn's disease as well as RA. Information was available for 96 of 131 women exposed to infliximab in relation to pregnancy. Of note, in 75% of the women concomitant medication exposure was documented. Of the known pregnancy outcomes, 67% of pregnancies resulted in live births and 15% ended in miscarriage including a 27-week stillbirth. The termination rate was 19% but none of the aborted fetuses was reported to have either major or minor anomalies. Of the five liveborn infants in this study with complications, one was delivered at 24 weeks gestation and died in the neonatal period of complications related to prematurity. This infant had also been exposed to azathioprine, mesalazine and metronidazole. One infant was born with congenital heart disease (Tetralogy of Fallot). Another infant of a mother with RA, who received leflunomide (a known teratogen in animals) in addition to infliximab, was found to have intestinal malrotation. Another infant had jaundice and respiratory distress but no malformations. One infant of a set of twins was reported to have developmental delay and hypothyroidism. The authors concluded that these outcomes were not significantly different from those expected in the general population, although they did acknowledge that their numbers were small. The authors concluded that the outcomes were similar to the general United States population of pregnant women and pregnant women not exposed to Crohn's disease.⁷

A retrospective chart review of 10 women treated with infliximab for induction or maintenance of remission in Crohn's disease during pregnancy reported that all 10 pregnancies resulted in live births with no congenital defects and no intrauterine growth restriction, although three infants were born prematurely.⁸

ADALIMUMAB

Adalimumab (Humira) is a recombinant human monoclonal antibody (IgG1) to TNF, which has been approved for the treatment of RA and psoriatic arthritis. It is also being used to treat other autoimmune disorders such as Crohn's disease. Adalimumab has a long half-life (approximately 2 weeks with a range of 10–20 days) and thus women need to take this into account if considering drug discontinuation when planning a pregnancy. The European Summary of Product Characteristics recommends that contraception be continued for at least five months after the last treatment.⁹ As with the other 'biological agents' there is relatively little information about its use and safety in pregnancy.

No developmental toxicity was seen in monkeys using intravenous doses of 30 mg/kg/week (and which resulted in serum drug concentrations greater than 100-fold higher than the maximum value expected during standard human therapy with 40 mg fortnightly).¹⁰

Preliminary data from the OTIS Autoimmune Diseases in Pregnancy Project show that 116 women were enrolled between January 2003 and May 2007.⁴ Of these, 27 women were exposed to adalimumab during pregnancy and met specific study criteria while an additional 47 women had

adalimumab exposure but were not eligible for enrolment in the prospective cohort study. This latter group included women treated for conditions other than RA including Crohn's disease, psoriatic arthritis, ankylosing spondylitis and non-specific auto-immune disorder. Outcomes after 26 exposed human pregnancies included two children with congenital malformations (undescended testes and microcephaly). There are at least six other case reports of pregnancy exposure resulting in normal outcomes.^{11–13}

ETANERCEPT

Etanercept is a soluble fusion protein comprised of a portion of the human TNF receptor and the Fc portion of human IgG1 and is administered via subcutaneous injection. There is one case report of a baby with VATER association (tracheo-oesophageal fistula, tracheal atresia, oesophageal atresia, imperforate anus, vertebral anomaly and a patent foramen ovale) born following a pregnancy during which the mother used etanercept 50 mg subcutaneously twice weekly throughout pregnancy to treat psoriasis and psoriatic arthritis.¹⁴

There are, however, several reassuring case reports of successful pregnancy outcomes in women taking etanercept to treat conditions such as systemic lupus erythematosus (SLE) and RA.^{15,16}

RITUXIMAB

Rituximab is a chimeric monoclonal antibody against the CD20 antigen on B-lymphocytes and has been mainly used for the treatment of non-Hodgkin's lymphoma and more recently for the treatment of RA and SLE.¹⁷ There is a case report of a child born following maternal exposure to rituximab to treat relapsed non-Hodgkin's lymphoma. Conception apparently occurred between the first two infusions and apart from mild anaemia the pregnancy was uncomplicated and resulted in the term delivery of a healthy infant who was well apart from mild transient neutropenia and lymphopenia.¹⁸ There is another case report of a normal pregnancy outcome following rituximab treatment in the second trimester, also for the treatment of non-Hodgkin's lymphoma.¹⁹

ABATACEPT

Abatacept (Orencia) is a recombinant CTLA4 analogue bound to an Fc receptor that modulates T-lymphocyte stimulation and is administered intravenously to treat moderate to severe RA.²⁰ It is not clear whether or not abatacept is actively transported across the human placenta. In rats, mice and rabbits embryofetal development was not affected by doses approximately 29 times the average human drug exposure. There is no information available regarding use of the agent in human pregnancy.

ANAKINRA

Anakinra (Kineret) is a recombinant non-glycosylated form of the human IL-1 receptor antagonist which has been used in the treatment of moderate to severe RA. Anakinra blocks the biological activity of IL-1 by competitively inhibiting IL-1 binding to the interleukin-1 type I receptor (IL-1RI), which is

expressed in a wide variety of tissues and organs. There have been no well-controlled studies in human pregnancy but studies on rats and rabbits have not shown impaired fertility or evidence of teratogenicity in doses up to 10 times the standard human dose.²¹ Given the lack of human pregnancy data this drug should only be used when all other treatment options have been exhausted.

CONCLUSION

While there is relatively limited information available about these new biological agents in pregnancy, the available information to date is relatively reassuring that they do not appear to pose a significant risk of teratogenicity. Unfortunately, it will take many years to obtain longer term follow-up data with regard to potential immunological or neurodevelopmental sequelae or effects on growth.

It is therefore important for practitioners and their patients to balance the potential benefits of these very effective newer drugs, which have few but reassuring data with regard to use in pregnancy, with the potential risks of untreated moderate and severe RA. The risk-benefit ratio may vary from case to case but it is important that doctors counsel their patients so as to inform them of their choices so that they can optimize their medications, ideally prior to conception.

It is hoped that sufficient data will be obtained from registries and studies such as the OTIS Autoimmune Diseases in Pregnancy Project so that in future women and their doctors will have better information on which to base important decisions regarding management of RA in pregnancy.

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