Therapy with Immunosuppressive Drugs and Biological Agents and Use of Contraception in Patients with Rheumatic Disease

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ABSTRACT. ***Objective.*** To investigate the attitude of patients towards immunosuppressive and biological drugs in relation to reproduction and the outcome of pregnancies exposed to these drugs.

Methods. We performed 2 postal surveys in regard to immunosuppressive drugs and reproduction, one in patients with rheumatic disease, the second in Swiss rheumatologists.

Results. Among the 237 female patients and the 189 male patients contacted for the survey, 72% of women and 40% of men returned the questionnaire. Ninety-four women and 47 men had received one or several immunosuppressive or biological agents during the years 2000-2005. Correct advice in regard to drugs and necessary birth control had been given to 84% of women. Advice to men was more inconsistent. One-third of women and 50% of men treated with potentially teratogenic drugs methotrexate (MTX) or leflunomide had not practiced birth control. The surveys of rheumatologists and patients disclosed 66 pregnancies under therapy with immunosuppressive and biological drugs with successful outcomes in 73%. However, 20% of pregnancies in women occurred under treatment with MTX and leflunomide.

Conclusion. Issues regarding drugs and reproduction are not always sufficiently discussed with female and male patients. The increasing use of combination therapies containing MTX necessitates ensuring that advice regarding birth control is followed in order to avoid pregnancies exposed to potentially fetotoxic drugs. (First Release May 15 2007; J Rheumatol 2007;34:1266–9)

Key Indexing Terms:
RHEUMATIC DISEASE IMMUNOSUPPRESSIVE DRUGS
BIOLOGICAL AGENTS REPRODUCTION PREGNANCY OUTCOME

Inflammatory rheumatic diseases occur for a majority of women and men in their reproductive years, at a time of life when many patients still have not completed their families. Drug treatment can therefore interfere with plans to have children or an already established pregnancy. In the last decade, drug therapy of rheumatic diseases has changed markedly with the introduction of new immunosuppressive drugs and particularly the use of biological agents[1]. Increasingly combination therapies are used, many of which include methotrexate (MTX). The challenge for the physician treating patients planning to have children is to adjust therapy to be compatible with pregnancy. This is often a difficult task since new drugs are never studied in pregnant or lactating women. Likewise, it is largely unknown whether immunosuppressive or biologic agents could affect the male gonads, with adverse effects on offspring of male patients. Possible effects of drugs on male and female reproduction are therefore unknown for a majority of substances, leaving both patients and physicians in uncertainty[2].

Knowledge on possible reproductive side effects of immunosuppressive drugs and biological agents is limited[3]. We analyzed data on reproduction from surveys of patients with rheumatic disease and of Swiss rheumatologists on the use of current immunosuppressive and biologic drugs before and during pregnancy. Our focus was on how frequently these drugs were used in patients of fertile age, what birth control was advised and practiced, and what the outcome was of pregnancies exposed to drugs. The aim was to improve pre-pregnancy counseling of patients planning to have children.

MATERIALS AND METHODS

Patient survey. Our study was approved by the Ethical Committee, University of Bern. A questionnaire on the use of antirheumatic drugs before and during pregnancy and an explanatory letter were sent to all patients with a diagnosis of inflammatory rheumatic disease who had been in contact with our specialized clinic for preconception counseling and pregnancy. The specialized clinic was established in 1999 and is open for all patients with rheumatic diseases who are planning to have children or are pregnant. Patients are either referred by their doctors to our outpatient clinic or make contact themselves. Inquiries regarding the effect of pregnancy on rheumatic disease and regarding antirheumatic drugs and reproduction are received from all over Switzerland.

The questionnaire was anonymous and could be returned in a prepaid envelope. No reminder was sent. The questionnaire contained the following items: age, type of rheumatic disease, disease duration, presence of any additional chronic disease (that could possibly influence pregnancy outcome either by the pathological process or by therapy), treatment with immunosup-

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pressive drugs during the period 2000-2005, advice received for birth control during therapy with immunosuppressive or biological drugs, and contraceptive practice during therapy. For the advice received in regard to contraception, the following options were given: No information received; or You must not become pregnant/father a child during therapy; or You have to use safe contraception throughout therapy, or throughout therapy and 3 months (or 6 months or 2 years) after withdrawal of the drug; or Other information (to be specified by the patient) was received. Options for the question on contraception practiced were: None practiced; irregularly practiced; or practiced according to the advice given as outlined above. For pregnancies exposed to immunosuppressive or biological drugs at conception or during the first trimester, outcome variables were asked for: abortion (induced and spontaneous), stillbirth, live birth, and birth defects.

A second anonymous questionnaire asking for the number of female and male patients with a pregnancy during the years 2002-2004 was sent to rheumatologists in Switzerland. A 2 year period was chosen to facilitate recall of relevant patients. The inquiry was limited to disease modifying and biological drugs and asked about pregnancy outcome of exposed pregnancies defined as spontaneous or induced abortion, stillbirth, live birth, and health of the newborn. The questions included: treatment with antimalarials, corticosteroids, azathioprine, salazopyrine, cyclosporine, leflunomide, MTX, and tumor necrosis factor (TNF)-α inhibitors during pregnancy. In case pregnancy had occurred during drug treatment, the outcome of pregnancy was recorded.

Since the risk for a negative pregnancy outcome is increased in systemic lupus erythematosus[4], antiphospholipid syndrome[5], mixed connective tissue disease, systemic sclerosis, and vasculitis[6], these diagnoses were excluded from the analysis of the surveys. Included were only pregnancy outcomes of patients with rheumatoid arthritis[7], ankylosing spondylitis[8], psoriatic arthritis, and juvenile idiopathic arthritis[7], diseases without an increased risk for miscarriage, stillbirth, or prematurity.

Definitions. Advice in regard to contraception was classified as correct or incorrect according to the guidelines for each drug containing information on use during pregnancy given by the Swiss Association of Rheumatologists. This information is freely accessible on the home page of the Association and conforms to the recommendations of a recent consensus paper on antirheumatic drugs and reproduction[3].

Statistics. Only descriptive statistics were applied.

RESULTS

Patient survey. Among the 237 female patients and the 189 male patients contacted, 170 (72%) women and 77 (40%) men returned the questionnaire.

The distribution of the different rheumatic diseases was similar in women and men (Table 1). Other additional chronic disease (diabetes mellitus, endocrine disease, allergic disease, hypertension, gastrointestinal disease) was present in 19% of women and 18% of men. A total of 94 (55%) women and 47 (64%) men had received one or several of the immunosuppressive and biologic agents listed in Table 2 during the years 2000-2005. Type of drug therapy and advice reported in regard to necessary contraception during and after therapy are shown in Table 2. Correct advice was reported by most female patients taking biologic agents whereas for 16% of cases treated with immunosuppressive drugs, the advice reported was incorrect. The uncertainty concerning possible mutagenic effects of antirheumatic drugs in men was reflected by the information reported (Table 2). Of 28 men taking MTX, 15 (54%) reported no advice for contraception. Contraception practiced during immunosuppressive therapy was reported by 83 female and 32 male patients. However, among patients treated with MTX or leflunomide, 9 women (27%) and 16 (48%) men had not practiced contraception.

Table 1. Characteristics of patients answering the questionnaire.

Characteristic	Women, N = 170 (%)	Men, N = 77 (%)
Rheumatoid arthritis	71 (41)	26 (35)
Ankylosing spondylitis	66 (39)	34 (44)
Psoriatic arthritis	11 (7)	11 (15)
Juvenile arthritis	11 (7)	3 (4)
Other arthritis*	11 (7)	3 (4)
Median age, yrs	35 (range 30–48)	46 (range 26–55)
Median disease duration, yrs	6 (range 1–36)	8 (range 1–37)

* Reactive arthritis, unspecified spondyloarthropathy, unspecified polyarthritis.

The female patients reported 34 pregnancies occurring during the use of salazopyrine (14), antimalarials (10), cyclosporine (1), azathioprine (1), leflunomide (1), MTX (3), combination of antimalarials and salazopyrine (1) and etanercept (3). Six pregnancies in partners of male patients were reported: 3 under therapy with TNF-α blockers and 3 with MTX. Outcomes of these pregnancies are shown in Table 3.

Survey of Swiss rheumatologists. Questionnaires and an explanatory letter were sent to the 409 rheumatologists registered in private practice in Switzerland. Twenty-seven letters were undeliverable due to wrong address. From the remaining 382, 131 rheumatologists returned the questionnaire (response rate 34%). Twenty-nine pregnancies during the intake of disease modifying antirheumatic drugs were reported by 24 rheumatologists, 19 in women and 10 in partners of men (one man taking salazopyrine + etanercept, one etanercept, 6 MTX, and 2 MTX in combination with TNF-α antagonists). Twenty-two pregnancies ended with a live born, healthy infant, 2 ended with miscarriage, 2 conceived during treatment with MTX had malformations, and 5 pregnancy outcomes were unknown (Table 4).

Major adverse events. Significant drug exposure during pregnancy occurred in 8 women taking MTX and 3 taking leflunomide (Tables 3, 4). Among the 11 men who received MTX at the time of conception, 2 children with congenital anomalies were born; one had atrophy of one hand and a small fistula beneath the ear, the other had anomalies of the toes (type not specified). Among women receiving other immunosuppressive drugs, one child of a mother treated with salazopyrine and prednisone had a small ventricular septal defect (Table 3).

DISCUSSION

The 2 surveys revealed current therapeutic practice of immunosuppression in patients with inflammatory rheumatic diseases in Switzerland. For the majority of antirheumatic drugs, the advice reported by female patients in regard to birth control was correct. This was particularly true for the biologic agents that are still the focus of attention. Contraception during immunosuppressive therapy was practiced by a major-

Table 2. Therapy with immunosuppressive drugs in female (F) and male (M) patients, advice regarding contraception and contraception practiced during 2000–2005 (results from the patient survey). Note that an individual patient may have received several drugs subsequently in the time period.

Drug	Sex		Contraception Advised		Contraception Practiced	
	F	M	F	M	F	M
Antimalarials	18	1	4	0	10	0
Sulfasalazine	20	3	5	1	8	3
Methotrexate (MTX)	26	28	24	13	16	14
Leflunomide	9	5	9	4	8	3
Combination therapy*	30	6	25	4	24	3
Other DMARD[a]	3	0	3	0	3	0
Infliximab	3	13	3	6	1	5
Etanercept	9	5	9	3	7	2
Adalimumab	1	0	1	0	1	0
Several TNF-α inhibitors	9	6	7	3	8	2

* Combination of antimalarials + sulfasalazine + MTX or antimalarials + sulfasalazine. [a] Cyclosporine (1), gold (1), azathioprine (1). DMARD: disease modifying antirheumatic drugs.

Table 3. Patient survey. Outcome of 34 pregnancies in women (F = female) and 6 pregnancies in partners of men (M = males) exposed to immunosuppressive or biologic agents at conception or during the first trimester. Results from the patient survey. Note that children with birth defects are included in the figures for live birth.

Outcome	Immunosuppressive Drugs*		Etanercept		Infliximab		Leflunomide		Methotrexate	
	F	M	F	M	F	M	F	M	F	M
No. of pregnancies	28	0	2	1	0	2	1	0	3	3
Miscarriage	2						1		1	
Induced abortion									2	1
Stillbirth										
Live birth	22		2	1		2				1
Birth defects	1[a]									
Outcome unknown	4									1

* Antimalarials, sulfasalazine, cyclosporine, azathioprine. [a] Infant with a small ventricular septal defect of a mother treated with sulfasalazine and prednisone.

Table 4. The survey of Swiss rheumatologists. Outcome of 19 pregnancies in women (F = female) and 10 pregnancies in partners of men (M = males) exposed to immunosuppressive or biological drugs at conception or during the first trimester. Note that children with birth defects are included in the figures for live birth.

Outcome	Immunosuppressive Drugs*		Etanercept		Infliximab		Leflunomide		Methotrexate	
	F	M	F	M	F	M	F	M	F	M
No. of pregnancies	8	0	3	2	1	0	2	0	5	8[a]
Miscarriage							1		1	
Induced abortion										
Stillbirth										
Live birth	7		3	1	1		1		1	8
Birth defects										2[b]
Outcome unknown	1			1					3	

* Antimalarials, sulfasalazine, cyclosporine, azathioprine. [a] Includes 2 patients on combination of MTX with TNF-α antagonists. [b] Includes one infant with atrophy of one hand and a small fistula beneath the ear, the other with anomalies of the toes.

ity of women and men. Most of the women treated with the potentially fetotoxic drugs MTX and leflunomide were advised to practice contraception during treatment and for some time after withdrawal. However, one-third of women did not follow the advice. The risk of congenital malformations after first trimester exposure to MTX has been recorded to be 10-17%[3,9] with the vulnerable period for the embryo at 6-8 weeks of gestation[10]. Whether leflunomide is a human teratogen is still unknown[11]. The unintended pregnancies that occurred during therapy with MTX and leflunomide show that information on birth control must be repeated and compliance must be ensured[12]. As shown by Chakravarty, *et al*[12], most doctors are aware of teratogenic risks of antirheumatic drugs and inform their patients accurately; however, only if information is recalled can compliance be ensured.

Advice on birth control reported by men was much more

inconsistent. Knowledge on mutagenic drug effects is limited and information is mostly based on theoretical grounds or animal data. No increase in the rate of malformations has been shown in epidemiological studies investigating effects of previous cytotoxic therapy on offspring of men[13]. In regard to biological agents, no data as to possible mutagenicity are available and the advice given to the men in our study reflects this uncertainty. The proportion of men not practising contraception while taking MTX and leflunomide was nearly 50%, although potentially harmful effects of these drugs on offspring of men is controversial and not proven[3,10]. The pregnancies that were reported during MTX treatment of men ended with the birth of healthy children, with 2 exceptions. Whether the observed 2 cases with malformations can be attributed to paternal MTX treatment cannot be answered with this study design. Available scarce experience in humans has not shown harmful effects of MTX on the testes[10,14]; whether MTX acts as mutagen is not clarified[10]. A similar consideration applies for the ventricular septal defect (VSD) that occurred in one pregnancy exposed to sulfasalazine. VSD is a rather common congenital heart defect and therefore a causal relationship to therapy cannot be proven.

There are several limitations to our study. First, the response rate of the physicians was low, however not lower than the overall response rate for other medical surveys and for a recent American survey on immunosuppressive drugs during pregnancy[12]. One reason for the limited response rate may be that specialists in private practice do not encounter pregnant patients frequently. Also, those rheumatologists who had no patient with a pregnancy under immunosuppressive therapy may not have felt it incumbent to return the questionnaire.

Regarding drug exposure before and during pregnancy, we had to rely on the patients' reports. Recall bias cannot be excluded, although one study did show a 62% correct recall of drug exposure identity, which was even better on chronic therapeutic exposure[15]. Since both patients and rheumatologists in Switzerland were surveyed, double reporting of pregnancy outcomes cannot be excluded. However, patients and rheumatologists were not questioned for precisely the same time period of pregnancy occurrence, so any overlap should be only partial. The results showed no double reporting for birth defects. In regard to the patient questionnaire, the response rate of male patients was only 40% compared to 72% in women. Since the response to surveys is related to the relevance for the recipient[16], the higher response rate in women may reflect the greater interest in the issue. Another explanation could be the higher median age of the men. Men who had completed their families may not have felt the need to answer questions on pregnancies during the last 5 years. This implies for our study that we can make no firm statements about men's attitude towards immunosuppressive drugs and birth control. Overall, the results of our study cannot be generalized to all arthritis patients taking these drugs, since it selected patients seeking advice on pregnancy issues from a specialized clinic.

Issues regarding drugs and reproduction need to be sufficiently discussed with female and male patients in order to avoid occurrence of pregnancies under therapy with possible fetotoxic drugs. Such therapy often raises great anxiety among exposed patients or their partners. In patients of fertile age planning for children should be taken into account before starting specific medications that may interfere with reproduction. Compliance with necessary birth control may require repeated confirmation.

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