Biological therapy in psoriatic patients whishing fatherhood: a multi-centre italian experience in real life

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F. Filippi[1], G. Odorici[2], A. Conti[2], V. Di Lernia[3], S. Di Nuzzo[4], M.A. Chessa[1*], M. Corazza[5], A. Patrizi[1], F. Bardazzi[1].

Affiliation:

[1] Department of Experimental, Diagnostic and Specialty Medicine, Division of Dermatology, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

[2] Department of Surgical, Medical, Dental and Morphological Sciences related to Transplant, Oncology and Regenerative Medicine, Dermatology Unit, University of Modena and Reggio Emilia, Modena 41124, Italy,

[3] Dermatology Unit, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia 42123, Italy

[4] Dermatology, Department of Medicine and Surgery, University of Parma, Parma 43126, Italy,

[5] Section of Dermatology and Infectious Diseases, Department of Medical Sciences, University of Ferrara, Ferrara, Italy

Corresponding author

Dr. Marco Adriano Chessa

Dermatology, Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna,

Via Massarenti 1 – 40138 Bologna, Italy

Tel: +39051-2144849; Fax +39-0512144867;

Email: marcoadriano.chessa@gmail.com

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DR. FEDERICA FILIPPI (Orcid ID : 0000-0001-8173-4257)

DR. GIULIA ODORICI (Orcid ID : 0000-0002-5910-8994)

DR. ANDREA CONTI (Orcid ID : 0000-0003-4848-3817)

PROF. ANNALISA PATRIZI (Orcid ID : 0000-0002-8398-0483)

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EDITOR,

Biological therapies have revolutionized the management of moderate-to-severe psoriasis in the last decade. However, if their impact on pregnancy outcomes has been recently investigated[1,2],data surrounding their effects after paternal exposure remain scarce and restricted to drugs initially introduced, such as the anti TNF-alfa agents[3,4]. In the literature, there is a lack of data regarding more recent biologics.

We performed a retrospective study in the Dermatologic Centers of 5 University Hospitals(Bologna, Modena,Reggio Emilia,Parma,Ferrara) in Emilia-Romagna(Italy), reviewing the medical records of 500 male patients with moderate-to-severe psoriasis, from 2009 to 2019.

We defined the father's exposure to biologic drug as after at least one administration before the time of conception.

We identified 32 male patients who fathered 38 children during biologic therapy(Table 1).The mean age at conception was 37±5.3 years(range 27-44),with a mean disease duration of 17.3±7.5 years(range 4-33).The mean period between first administration and pregnancy for each child was 4.02±2.8 years(range 0.5-10).

In 30 patients anti TNF-alfa agents had been administrated (13 were treated with infliximab, 8 with etanercept and 9 with adalimumab).Five patients had been prescribed an anti IL-

12/23 drug(ustekinumab) and 3 were under therapy with anti IL-17 monoclonal antibody(secukinumab). None of them had adverse events during treatment.

Most patients conceived only one child during biological therapy.We report 4 cases of elective abortion in the female partner for personal reasons, and 1 partner with 2 spontaneous abortions.

No unhealthy infants were observed in this cohort:no congenital or cognitive disorders were observed at birth and until the time of writing(maximum follow up period:10 years).None of our male patients required fertility assistance.

At present, what do we know about psoriasis and male fertility?

Recent evidence indicates that psoriasis, like other diseases with a systemic state of inflammation,

may impair male fertility. In fact, psoriatic patients more frequently have an altered sex hormone serum profile(low free testosterone, high oestrogens levels) compared to unaffected subjects. This, in turn, might have an impact on the inflammation itself, worsening the psoriasis, because of the role of androgens in anti-inflammatory activities[5].

The second interesting question is: what do we know about biologics and male fertility?

The Food and Drug Administration categorized medications into 5 pregnancy risk categories, and biologics received a category B rating(animal studies did not reveal gonadal toxicity).This classification considers potential teratogenicity and infertility from maternal, but not paternal, exposures. This information gap makes the administration of biologics to male patients wishing fatherhood a difficult field for dermatologists.

A recent review[4] reports reassuring data on fathers exposed to anti TNF-alfa at time of conception; these drugs seem to increase sperm vitality and motility, probably because of the negative effects of TNF-alfa on the integrity of the sperm membrane and the sperm motility[6-8].In line with these evidences, in our sample 30 patients were receiving anti TNF-alfa agents, and no unhealthy infants were observed.

Interestingly, in our case series 8 patients were receiving anti IL-12/23 or anti IL-17 drugs,and also these patients had fathered healthy children with normal growth.

In the literature,there are some data regarding pregnancy occurred in mother treated with secukinumab or ustekinumab[1] which offer reassurance in cases of conception, since no evidence of adverse pregnancy outcome has been recorded. In contrast, to our knowledge, data on male fertility in humans are absent[9,10] and only animal studies were conducted,

without any impairment of fertility reported. Our innovative results suggest that conception during administration of these drugs is safe. Limitations of this study are:(i)the small number of subjects;(ii)we did not investigate the causes of 2 spontaneous abortions in our sample;(iii)the real influence of biological therapy on male fertility is still unclear.

In conclusion, this study reports our real-life experience in prescribing biologic agents and provides some evidence of reassurance in male patients concerning fertility and fatherhood. Our aim is to support dermatologists in the use of biologic drugs also in male patients looking to conceive.

Nevertheless,larger and prospective studies are necessary to properly guide clinicians in their therapeutic decisions.

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Table 1. Characteristics of male patients with psoriasis who fathered children during biologic therapies.

MALE PATIENT ID	AGE AT CONCEPTION (years)	DISEASE DURATION (years)	DRUG	NUMBER OF PARTNER PREGNANCIES	PERIOD BEFORE FIRST ADMINISTRATION AND PREGNANCY FOR EACH CHILD (years)	NEWBORNS	HEALTHY NEWBORNS	AGE OF CHILD (years)
1	36	19	Ustekinumab	1	1	1	1	3
2	29	4	Adalimumab	1	2	1	1	7
3	35	15	Adalimumab	1	3	1	1	6
4	32	10	Etanercept	1	2	1	1	7
	35	13	Ustekinumab	1	2	1	1	1
5	37	17	Ustekinumab	1	1	1	1	1
6	31	10	Infliximab	1	4	1	1	7
7	29	5	Adalimumab	1	1	1	1	8
8	36	15	Infliximab	2(1 elective abortion)	4	1	1	9
	44	23	Secukinumab	1	1	1	1	1
9	30	5	Infliximab	1	4	1	1	6
10	29	4	Adalimumab	1	2	1	1	5
11	33	12	Etanercept	1	3	1	1	5
	38	16	Secukinumab	1	0.5	1	1	6 months
12	28	10	Infliximab	1	4	1	1	8
13	41	20	Secukinumab	1	1	1	1	1
14	39	14	Adalimumab	1	7	1	1	3
15	40	25	Ustekinumab	1	2	1	1	5 months
16	38	18	Etanercept	2(1 elective abortion)	5	1	1	3
17	40	22	Infliximab	3(2 elective abortion)	8	1	1	1
18	27	20	Infliximab	1	5	1	1	10
	35	28	Ustekinumab	1	1	1	1	3
19	37	30	Adalimumab	3(2 spontaneous abortion)	6	1	1	1
20	41	29	Adalimumab	1	6	1	1	4

	43	31	Adalimumab	1	8	1	1	2
21	35	22	Infliximab	1	2	1	1	10
	37	24	Infliximab	1	4	1	1	8
22	41	21	Etanercept	1	6	1	1	9
23	43	12	Etanercept	1	8	1	1	5
24	41	17	Infliximab	1	7	1	1	3
25	41	33	Infliximab	1	10	1	1	4
26	42	18	Adalimumab	1	1	1	1	5 months
27	44	20	Infliximab	1	1	1	1	2
28	42	15	Etanercept	1	0.5	1	1	10
29	51	20	Etanercept	1	6	1	1	10
30	35	12	Etanercept	1	8	1	1	1
31	34	14	Ustekinumab	1	4	1	1	2
32	36	10	Infliximab	1	5	1	1	4