JDDG

Journal of the German Society of Dermatology

CME Article

DOI: 10.1111/ddg.12596

Submitted: 26.10.2014
Accepted: 12.12.2014
Conflict of interest
None.

# New systemic agents in dermatology with respect to fertility, pregnancy, and lactation

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Section Editor
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## Summary

With the increasing use of new, predominantly biologic drugs in dermatology, questions frequently arise in clinical practice as to their safety in women wishing to conceive as well as during pregnancy and lactation. Apart from the Summary of Product Characteristics and the Physician's Desk Reference, reliable information may be obtained from databases such as the one compiled by the Center for Pharmacovigilance and Consultation on Embryonal Toxicology at Charité University Medical Center Berlin (https://www.embryotox.de). Another source of information is researching recent publications, for example via PubMed (http://www.ncbi.nlm.nih.gov/pubmed).
This article presents current knowledge from the sources mentioned above, and gives detailed information about the use of new biologic agents in women wishing to conceive as well as during pregnancy and lactation. Drugs reviewed include: infliximab, adalimumab, etanercept, metastatic for psoriasis, vemurafenib, dabrafenib, imatinib, ipilimumab for melanoma, vismodegib for basal cell carcinoma, rituximab for cutaneous lymphoma as well as omalizumab and anakinra used in the treatment of allergies.

## Introduction

In recent years, a number of new, specific systemic therapies have been introduced in dermatology. Since they are based on completely novel principles, physicians are facing additional challenges such as drug-specific preliminary tests, familiarity with inclusion and exclusion criteria for drug administration, and the management of novel adverse effects. In everyday clinical practice, possible effects on fertility are often not considered, including the fact that patients should be offered the option of oocyte and sperm cryopreservation. There is a great amount of uncertainty with regard to the administration of these new substances during pregnancy and lactation. Not even excellent online databases such as the one compiled by the Center for Pharmacovigilance and Consultation on Embryonal Toxicology at Charité University Medical Center Berlin (https://www.embryotox.de) fully cover all potential questions. Table 1 gives an overview of the terminology used in this context.

In general, data relating to reproduction is very limited, because – for ethical reasons – patients planning to have children as well as pregnant and lactating women are not enrolled in approval studies. In vitro models, however, do not reflect any systemic repair mechanisms. In addition, due to the species specificity of

 

**Table 1** Overview of terms used with respect to potential adverse effects of drugs on reproduction.

| | |
|---|---|
| Reproductive toxicity | Impairment of fertility and/or damage to the unborn child |
| Genotoxic | A term used in pharmacology for determining toxicity: *in vitro* induction of DNA alterations; does not necessarily mean mutagenic activity in vivo |
| Mutagenic | Induction of mutations/chromosomal aberrations (genetic damage) |
| Teratogenic | Induction of malformations in the embryo |
| Embryotoxic | Damage to the child during the embryonic phase (5th to 8th week of gestation, organogenesis). Depending on the severity, the result is either growth retardation, malformations (teratogenicity), or death of the embryo |
| Fetotoxic | Damage to the child after the embryonic phase (from the 9th gestational week onwards) |

antibodies, standard animal studies are not possible in the case of biologics. Thus, it is necessary to resort to analogous, for instance murine, antibodies with the same target structure or testing of high doses on cynomolgus monkeys. The objective of the present article is to offer an overview of the current body of evidence regarding the use of the new systemic dermatological therapies in couples wishing to conceive as well as during pregnancy and lactation.

## Psoriasis

In addition to various topical treatment options and phototherapy (UVB, PUVA), standard psoriasis therapies already include a number of systemic agents. Table 2 gives an overview of their use in couples wishing to conceive as well as during pregnancy and lactation.

In recent years, a growing number of biologics has become available to psoriasis patients who either do not adequately respond to standard therapies or do not tolerate them because of adverse effects. These include tumor necrosis factor (TNF) inhibitors infliximab, etanercept, and adalimumab, as well as the interleukin12/23 p40 inhibitor ustekinumab. They are either monoclonal antibodies (infliximab, adalimumab, ustekinumab) or fusion proteins (etanercept).

Similar to maternal antibodies, biologics cross the placenta. The active transport into the fetal circulation commences during the 14th week of gestation and involves the Fc receptor on the trophoblast cells. Treating the mother in the 2nd and 3rd trimester may lead to high drug concentrations in the fetus.

Similar to maternal antibodies, biologics cross the placenta. Due to their size, simple diffusion is unlikely; instead, they cross the placenta by active transport via the Fc receptor on the trophoblast cells and enter the fetal circulation [1]. This active placental transport starts during the 14th week of gestation. Treating the mother in the 2nd trimester may already lead to high drug concentrations in the fetus, sometimes exceeding maternal serum concentrations in the third trimester, especially in the case of adalimumab and infliximab [2]. Immunoglobulins have a longer half-life in neonates of up to six months.

### Infliximab (Remicade®, biosimilars: Remsima®, Inflectra®)

Infliximab is a recombinant chimeric human-murine monoclonal IgG1 antibody. Remicade® is approved for the treatment of moderate to severe plaque psoriasis

  

**Table 2** Use of conventional systemic treatment options for psoriasis in patients wishing to conceive as well as during pregnancy and lactation.

| | Fertility Man | Intake at conception (♂) | Fertility Woman | Intake at conception (♀) | Pregnancy | Lactation |
|---|---|---|---|---|---|---|
| Fumaric acid | Unimpaired (data from animal experiments) | Possible | Unimpaired (data from animal experiments) | Data insufficient, not mutagenic, not embryotoxic | Data insufficient, not mutagenic, not embryotoxic | Not studied |
| MTX | Impaired | Not recommended (potentially mutagenic) | Impaired | Contraindicated (genotoxic/ potentially mutagenic) | Contraindicated | Contraindicated |
| Cyclosporine A | Reversible impairment possible | Possible | Reversible impairment possible | Possible (not mutagenic, not teratogenic) | Possible after carefully weighing risks and benefits* | Possible after carefully weighing risks and benefits* |
| Retinoids | Reversible impairment possible | Possible | Not studied | Contraindicated | Contraindicated | Contraindicated |

*This generally applies to mothers who have received an organ transplant

in patients who have not responded to other systemic therapies or PUVA, or who have a contraindication or are intolerant to such therapies. Remicade® is also used in psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis (in combination with methotrexate) as well as in Crohn's disease and ulcerative colitis following inadequate response to conventional disease-modifying antirheumatic drugs (DMARDs).

On the basis of a pharmacokinetic study in patients with ankylosing spondylitis and a non-inferiority study of patients with rheumatoid arthritis, the European Medicine Agency, in 9/2013, approved the two biosimilars Remsima® and Inflectra® for the other mentioned indications as well. However, they are not available in Germany until the extended Remicade® patent expires in 2/2015. There is currently no data on reproductive toxicity for either of these drugs, the following information only applies to Remicade®.

Data on the effects of Remicade® on fertility is limited. High TNFα concentrations result in a loss of sperm motility and induction of apoptotic DNA fragmentation. In vitro experiments have shown positive effects of TNFα blockade by infliximab on sperm motility as well as on the integrity of its membrane and chromatin [3]. Normal ejaculate findings remained unchanged in patients on infliximab [4]. Small case series have described births of healthy children from fathers who were on Remicade® at the time of conception [5]. The female fertility does not seem to be affected by infliximab, either. Rheumatic women with severe disease activity also benefit from infliximab in terms of their fertility. By contrast, the Summary of Product Characteristics (SPC) of Remicade® contain data on mice that received an (analogous) murine TNF-α inhibitor and subsequently showed a decrease in the number of pregnant animals. However, it remains unclear whether this was due negative effects on male or female animals.

 

Although there is registry data on approximately 450 prospectively registered pregnancies on Remicade® and, in line with data obtained from animal studies, no embryotoxic effects of the drug have been detected, the SPC nevertheless recommends that women of childbearing age use adequate contraception during therapy with Remicade® and for six months after the last infusion. Overall, 1,000 pregnancies while on Remicade® have been documented, most of them in the 1st trimester [2].

Infliximab does not affect female or male fertility. It is neither genotoxic nor embryotoxic. In contrast to the SPC, conception while on infliximab therefore appears acceptable in both men and women according to current data.

In addition to the knowledge about the lack of active transport in the first trimester, the Center for Pharmacovigilance and Consultation on Embryonal Toxicology at Charité University Medical Center Berlin assesses the existing experience differently and sees no need to discontinue Remicade® in couples who are trying to conceive.

After the 20th week of gestation, the administration should be limited to cases with a strict indication due to the active transport into the fetal circulation via the Fc receptor on the trophoblast cells. After the 30th gestational week, therapy with infliximab should be discontinued, as fetal serum levels are very high from this point onwards. Median values in the cord blood of newborns were 160% of the corresponding infliximab serum levels in the mother [2]. The drug remained detectable in the serum of infants for another 6 months, exposing them to a significantly increased risk of infection. For up to six months postpartum, live vaccines are therefore contraindicated in babies exposed during pregnancy. According to the current vaccination schedule of the Robert Koch Institute, in Germany, this would only affect the oral vaccination for rotavirus. There has been a case report of a fatal infection with the BCG vaccine virus in a four-month-old infant whose mother had received infliximab for Crohn's disease during pregnancy [6].

Active transplacental transport in the 2nd / 3rd trimester leads to infant serum levels significantly higher than maternal levels. For the infant, this means an increased risk of infection and a contraindication for live vaccines in the first 6 months of life. Contrary to the SPC, breastfeeding is possible due to low oral bioavailability of infliximab after considering all alternatives.

Just like any human immunoglobulin, infliximab is excreted into breast milk, but levels are much lower than those in maternal serum. A few days after the infliximab infusion, the highest values measured in breast milk amounted to 2–5 % of serum levels [1]. In addition, the oral bioavailability in infants is low. In nursing infants of mothers who received infliximab only during lactation and not during pregnancy, infliximab was not detectable in serum [1].

Nevertheless, according to the SPC, women should not breastfeed for at least six months after the treatment with Remicade®. The Center for Pharmacovigilance and Consultation on Embryonal Toxicology at Charité University Medical Center Berlin considers breastfeeding acceptable when Remicade® is determined to be the most appropriate medication for the patient after careful consideration of possible alternatives.

## Adalimumab (Humira®)

Adalimumab is a human monoclonal antibody (IgG1) against TNF-α that binds and neutralizes the cytokine. Humira® is approved for the treatment of moderate to severe plaque psoriasis in patients who have not responded to other systemic therapy or PUVA, or who have a contraindication or do not tolerate such therapies. Humira® is also used in psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, and polyarticular juvenile idiopathic arthritis as well as in Crohn's disease and ulcerative colitis after inadequate response to conventional DMARDs.

No preclinical studies exist on the effects of adalimumab on fertility. Clinical data is very limited and does not indicate any negative impact on male or female fertility. In men, spermiogram parameters remained unchanged [7], while in women with rheumatoid arthritis, the decrease in inflammation even resulted in improved fertility [8]. Adalimumab is not genotoxic. Nevertheless, due to limited

  

data, the SPC recommends contraception during Humira® therapy and within five months after the end of treatment.

There is available data obtained from the product registry, case series and case reports on roughly 300 pregnancies while on adalimumab. In approximately 200 evaluated pregnancies, there was no evidence of teratogenic effects after administration of Humira® in the first trimester. Neither an increased rate of malformations nor miscarriages have been reported [2]. In the 2nd-3rd trimester, adalimumab passes into the fetal circulation, similar to maternal IgG1. Due to the active transport via the Fc receptor on the trophoblast cells, median values in the cord blood of newborns measured immediately postpartum were higher than corresponding maternal serum levels (median 179 %) [2]. Hence, similar to the situation with Remicade®, the infant is at an increased risk of infection after intrauterine exposure in the 2nd /3rd trimester. According to the current SPC for Humira®, live vaccines should not be administered to babies within five months after the last adalimumab injection during pregnancy. Children exposed in utero have thus far not displayed any clinical abnormalities [2].

Contrary to the SPC and based on current trial data, the Center for Pharmacovigilance and Consultation on Embryonal Toxicology at Charité recommends that adalimumab need not necessarily be discontinued prior to pregnancy in women wishing to conceive. From the 20th week of gestation onwards, the risks and benefits of continued adalimumab treatment must be carefully weighed, whereas therapy should definitely be discontinued after the 29th gestational week.

Adalimumab serum levels of children drop postnatally, even if the mother continues to receive the medication and breastfeeds. This is due to the low oral bioavailability. Anecdotal reports have demonstrated concentrations of 0.1 % of maternal serum levels in the breast milk, but negative effects of breastfeeding during therapy with Humira® are not known due to very limited data. Nevertheless, the SPC (still) recommends that Humira® not be administered during breastfeeding. Women should not breastfeed within five months after the last injection. By contrast, the Center for Pharmacovigilance and Consultation on Embryonal Toxicology at Charité deems the infant's risk of breastfeeding during therapy with Humira® negligible. Thus, breastfeeding is acceptable if adalimumab is determined to be the best medication for the patient after careful consideration of possible alternatives.

For adalimumab, the same statements hold true as for infliximab with respect to its use in women wishing to conceive as well as during pregnancy and lactation.

## Etanercept (Enbrel®)

The TNF-α inhibitor etanercept is a chimeric fusion protein consisting of the extracellular ligand-binding domain of the TNF receptor 2 and the Fc region of IgG1. The active substance is approved for the treatment of moderate to severe plaque psoriasis in patients who have not responded to other systemic therapy or PUVA, or who have a contraindication or do not tolerate such therapies. Enbrel® is also used in psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, and polyarticular juvenile idiopathic arthritis after inadequate response to conventional DMARDs.

Etanercept has no negative effects on male or female fertility. It is neither mutagenic nor teratogenic. In contrast to the SPC, and in line with current data, conception while on Etanercept seems acceptable for both men and women.

Etanercept has no negative effects on fertility. Many studies have revealed unchanged spermiogram parameters on Enbrel® [4, 7]. In infertile women with increased NK cell numbers or Th1-mediated subfertility, etanercept has been successfully used periconceptionally [8]. Etanercept is not mutagenic.

No evidence of teratogenicity has been collected in over 500 followed pregnancies during therapy with Enbrel®. Most exposures occurred in the 1st trimester. No increased rates of malformations or miscarriages have been observed [2].

 

A potential association with complex malformations (VACTERL) could not be confirmed. Nevertheless, after exposure during organogenesis, a high-resolution ultrasound examination (detailed fetal scan) should be performed.

The experience with the administration in the 2nd and 3rd trimester is limited. An effect on the immune response of exposed children with increased risk of infection is suspected. Therefore, according to the SPC for Enbrel®, live vaccines should not be administered in these children before the age of four months.

The active transport of etanercept across the placenta into the fetal circulation is less pronounced than that of infliximab and adalimumab

The active transport of etanercept across the placenta into the fetal circulation is less pronounced than that of infliximab and adalimumab. Nevertheless, significant levels of etanercept were detected in cord blood of newborns (median: 6 % of maternal serum levels). They continuously decrease postpartum, even when the mother is breastfeeding and continues to receive the medication [2]

Administration of etanercept during breastfeeding is thought to be acceptable due to insignificant excretion into breast milk and the lack of bioavailability in term infants.

Administration of etanercept during breastfeeding is thought to be acceptable due to insignificant excretion into breast milk and the lack of bioavailability in term infants. Serum levels of etanercept in breastfed infants were 1/800 of maternal serum levels. The SPC indicates that both the benefit of breastfeeding for the baby and the benefit of therapy for the mother should be considered when deciding for or against administration during breastfeeding.

## Ustekinumab (Stelara®)

Ustekinumab is a monoclonal IgG1 antibody that binds to the p40 subunit of interleukins (IL) 12 and 23, thereby inhibiting them. In January of 2009, Stelara® was approved for the treatment of moderate to severe plaque psoriasis in cases where other systemic therapies, including PUVA, do not yield desired therapeutic results, or are contraindicated or not tolerated. In addition, Stelara® is approved for psoriatic arthritis inadequately responsive to prior therapy with a non-biologic DMARD.

There are only preclinical animal studies on the effects of ustekinumab on fertility. Reproductive toxicity studies in cynomolgus monkeys revealed no impairment of male fertility. Use of an analogous IL-12/23 antibody in mice showed no adverse effects on female fertility indices. Therefore, fertility-protective measures need not necessarily be offered. However, in women wishing to conceive, the use of the more thoroughly investigated TNF α inhibitors is recommended instead.

As ustekinumab is a human IgG1 just like adalimumab and infliximab, transplacental passage by active transport in the 2nd / 3rd trimester is likely. Thus far, this has not been studied in humans.

There are isolated case reports on the use of Stelara® during pregnancy. Two pregnant women received Stelara® periconceptionally and at the end of the 1st month of pregnancy, without this having a negative impact on embryonic and fetal development, both babies were healthy term babies [9]. Another patient with severe pustular psoriasis was receiving Stelara® during her entire pregnancy without any observed adverse effects on pregnancy and the baby's health [10]. By contrast, there is another case report of an unplanned pregnancy during therapy with ustekinumab in a 35-year-old woman. Despite immediate discontinuation of therapy, she had a miscarriage in the 12th gestational week [11]. All in all, there is no sufficient data on the use of ustekinumab in women wishing to conceive and during pregnancy; hence, administration to pregnant women should be avoided if possible. According to the SPC, women of childbearing age should use effective birth control methods during treatment and for at least 15 weeks after the end of therapy.

There is no clinical experience as to the use of Stelara® during breastfeeding. Animal studies have shown that ustekinumab is excreted in human milk in small amounts. It is not known whether ustekinumab is absorbed systemically in the

  

There is no sufficient data as to the use of ustekinumab in women wishing to conceive as well as during pregnancy and lactation. In these cases, the aforementioned TNFα inhibitors should therefore be used if therapy is required.

infant. The oral bioavailability of the antibody is probably low. Therefore, the SPC for Stelara® recommends careful consideration of the benefits of breastfeeding for the child and the benefits of Stelara® therapy for the mother in a period of up to 15 weeks after the last dose of the drug.

## Dermatologic oncology

Individualized therapies have been introduced in almost all areas of dermatologic oncology and allow for a more effective treatment of diseases. Older agents still frequently used in dermatologic oncology are listed in Table 3.

### Vemurafenib (Zelboraf®)

Vemurafenib selectively inhibits the mitogen-activated protein kinase (MAPK) signaling pathway in BRAF V600E/K/D mutant melanoma cells and thereby induces (temporary) tumor regression. After the discovery of the MAPK signaling pathway-activating V600E mutation in the BRAF oncogene, the substance had been tested in clinical studies since 2008, before its approval for the treatment of unresectable or metastatic melanoma in August of 2011 (USA) and in February of 2012 (Europe).

Its use in other tumor entities, which also have an underlying BRAF V600 mutation, such as some forms of lung cancer, thyroid cancer, brain tumors, and hairy cell leukemia is still under investigation after promising initial results.

Toxicity studies with repeated administration of therapeutic doses of vemurafenib to rats and dogs revealed no histologic changes in ovaries and testes (SPC Zelboraf®). However, this data is not sufficient. As the use of a similar BRAF inhibitor (dabrafenib, see below) has already been shown to be associated with a potentially irreversible damage in spermatogenesis, men who want to have children should be offered the option of sperm cryopreservation prior to starting treatment with vemurafenib.

In animal studies with rats and rabbits, the drug has been shown to cross the placenta, without displaying any teratogenic effects, though. Excretion into breast milk has not been investigated. There is currently no clinical data available with regards to conception while on vemurafenib and its use during pregnancy and lactation. There has only been one report documenting the administration of

**Table 3** Use of conventional dermatooncologic drugs in patients wishing to conceive as well as during pregnancy and lactation.

| | Fertility Man | Intake at conception (♂) | Fertility Woman | Intake at conception (♀) | Pregnancy | Lactation |
|---|---|---|---|---|---|---|
| Dacarbazine | Impaired | Not recommended | Impaired | Contraindicated | Contraindicated | Contraindicated |
| interferon alpha | In low-dose administration probably unaffected | no data | Impaired (animal studies) | Contraindicated (potentially fetotoxic ) | Contraindicated (potentially fetotoxic ) | Contraindicated |
| Cyclophosphamide | Sometimes: irreversible impairment | Not recommended (potentially mutagenic) | Impaired | Contraindicated (teratogenic) | Contraindicated (teratogenic) | Contraindicated |
| Bexarotene | Not impaired | Possible | Not impaired | Contraindicated (teratogenic) | Contraindicated (teratogenic) | Contraindicated |

 

vemurafenib for metastatic melanoma during pregnancy (25th-30th week). During this period, the fetus' preexisting growth retardation intensified. After Cesarean section, the child recovered and is now healthy. However, the mother died 2.5 months later [12].

The effects of vemurafenib on fertility are unclear. The use in pregnancy should be limited to life-threatening cases (consider premature Cesarean section), and nursing mothers should stop breastfeeding.

The SPC for Zelboraf® recommends contraception for women of childbearing age for six months after discontinuing the drug. It should be noted that, due to CYP3A4-mediated metabolism, the plasma availability and thus the effect of hormonal contraceptives may be reduced in patients on vemurafenib.

## Dabrafenib (Tafinlar®)

Approved in 2013, dabrafenib is the second inhibitor of the V600E, V600K, and V600D mutant BRAF oncogene for the treatment of unresectable or metastatic melanoma.

There is no experience as to the use of dabrafenib at the time of conception and during pregnancy and lactation. It is not known whether this drug passes into breast milk. Dabrafenib is not mutagenic. In contrast to vemurafenib, animal studies in rats and dogs have shown reproductive toxicity. Even at low doses, dabrafenib leads to a potentially irreversible reduction in spermatogenesis. In pregnant rats, the number of corpora lutea was reduced. Men and women who want children should therefore be offered the possibility of cryopreservation of their gametes prior to dabrafenib therapy with.

Dabrafenib impairs fertility and is teratogenic. Patients wishing to conceive should be offered the possibility of cryopreservation of gametes prior to therapy. Its use during pregnancy and lactation is contraindicated.

In addition, dabrafenib is teratogenic and affects embryonic/fetal development. Women of childbearing age must use effective contraceptive methods during treatment and, according to the SPC, also up to four weeks after the end of treatment. Similar to vemurafenib, the reduced effectiveness of hormonal contraceptives has to be observed; hence, alternative methods should be used.

## Ipilimumab (Yervoy®)

Ipilimumab is a human monoclonal anti-CTLA4 antibody (IgG1) that blocks the inhibition of T cell activation, resulting in a strong activation of the (antitumor) T cell response. The drug has been approved for the treatment of unresectable or metastatic melanoma since 2011 (2012 in Europe). Its use in the treatment of lung and renal cell cancer as well as metastatic prostate cancer is currently being tested.

Preclinical animal data on reproduction toxicity showed a decreased testicular volume in patients on ipilimumab, without any histologic correlate (SPC Yervoy®). There is no data on the direct effects of the drug on human fertility. However, ipilimumab may impair fertility as a result of immune-mediated endocrinopathy. In study cohorts, hypophysitis was observed in 0–17% of patients [13], especially in men. Serum levels of ACTH, STH, prolactin, TSH, LH, and FSH, as well as the dependent hormones thyroxine and testosterone drop by varying degrees. Clinical symptoms are nonspecific: patients complain of headache, blurred vision, fatigue, insomnia, difficulty concentrating, mood swings, but also erectile dysfunction and loss of libido. An autoimmune hypophysitis secondary to CTLA4 blockade typically begins two to six months after the start of ipilimumab therapy. The diagnostic workup consists of hormone analysis and MRI. Therapy includes high-dose corticosteroids, which quickly reverse the inflammation. The pituitary function, however, may remain impaired for longer, some patients require lifelong hormone substitution (most of the time only corticosteroids). Without substitution, low FSH and LH levels lead to infertility due to the lack of oocyte and sperm maturation.

Ipilimumab may impair fertility as a result of immune-mediated hypophysitis.


 

This should be primarily considered in the substitution of testosterone (men) and estrogen (women).

In pregnancy, due to the increased risk of miscarriages, stillbirths, and premature births, ipilimumab should only be given in consultation with the future parents after a rigorous benefit-risk assessment.

To date, there has been no clinical experience with the use of ipilimumab in pregnant women and nursing mothers. As an IgG1, ipilimumab crosses the placental barrier. In pregnant monkeys, ipilimumab led to a dose-dependent increase in miscarriages, stillbirths, and premature births. The mortality rate among the offspring was increased, and there is a questionable association with malformations of the urogenital tract. Therefore, the use of ipilimumab is not recommended during pregnancy and in women of childbearing age who are not using contraception, unless the clinical benefit outweighs potential risks. Ipilimumab is excreted into human breast milk in small quantities. Due to the low oral bioavailability of IgG, only low systemic exposure of the infant would be expected. Nevertheless, weaning is recommended, as adequate infant formulas are available.

### Imatinib (Glivec®)

Imatinib is an ATP analog that competitively and selectively blocks the ATP-binding site of specific tyrosine kinases (including c-kit, bcr-abl, and the PDGF receptor). This active substance is widely used for hematologic cancers (for example, in bcr-abl-positive leukemias, myelodysplastic syndrome, and hypereosinophilic syndrome). In dermatology, imatinib is approved for the treatment of adult patients with unresectable and/or recurrent and/or metastatic dermatofibrosarcoma protuberans. In addition, a phase II study showed a response to imatinib in metastatic mucosal, acral, and lentigo maligna melanoma with c-kit mutations (not amplifications).

Despite the absence of controlled clinical studies on the effects of imatinib on male fertility, there are numerous case reports showing that the drug can impair sperm quality, especially the sperm count (including azoospermia). However, about 40 pregnancies have been published with the father taking imatinib. Three of these 40 pregnancies resulted in a miscarriage, two others resulted in an abortion, and intestinal malrotation was observed in one child. Thus, as a precaution, sperm cryopreservation should be performed prior to the start of therapy in couples trying to conceive [14].

Cryopreservation of gametes should be offered to patients prior to initiation of imatinib therapy.

In animal experiments Glivec® was assessed to be teratogenic and should not be used during pregnancy according to the manufacturer. Two intermediate substances in the manufacturing process, which can also be detected in the final product, are potentially mutagenic. To date, the Center for Pharmacovigilance and Consultation on Embryonic Toxicology at Charité has not listed Glivec®, but there are smaller case series on its use in pregnancy. Clinical courses are either unremarkable or show minor malformations (clinodactyly, hypospadias) and an increased miscarriage rate [15]. Until further information becomes available, administration of imatinib during pregnancy should be limited to cases that inevitably require its use. Accordingly, patients should be adequately informed.

Because of its teratogenicity (minor malformations possible), imatinib should only be used during pregnancy if absolutely necessary and after the patient has been adequately informed. After pregnancy, weaning is recommended.

Imatinib and its metabolites are excreted into human breast milk. In nursing infants, approximately 10% of maternal drug levels are reached. Thus, weaning is required.

### Vismodegib (Erivedge®)

Vismodegib is used in the treatment of inoperable, locally advanced basal cell carcinoma not suitable for radiation therapy as well as in metastatic basal

 

cell carcinoma. With respect to reproductive age, this is particularly relevant to patients with Gorlin-Goltz syndrome. The active substance inhibits the hedgehog signaling pathway by blocking the transmembrane receptor SMO (smoothened).

This signaling pathway plays an important role in embryonic development and, as expected, preclinical animal studies revealed embryonal mortality rates of 100 % at therapeutic doses. Lower doses led to severe malformations. The use of vismodegib in pregnancy is thus contraindicated. Women of childbearing age must participate in a pregnancy prevention program (at least two different contraceptive methods, and a mandatorily negative pregnancy test under medical supervision in the week before the start of therapy) prior to initiation of vismodegib treatment and 24 months after treatment.

Moreover, vismodegib can be found in sperm. To avoid potential fetal exposure during pregnancy, male patients should not have unprotected sex with pregnant women for up to two months after the last dose. The passage of vismodegib into human breast milk has not been studied. Due to the risk of causing serious developmental problems, women should not breastfeed during therapy and 24 months after the last dose (SPC Erivedge®).

Vismodegib is contraindicated in couples wishing to conceive as well as during pregnancy and lactation. Due to negative effects on fertility, patients should be offered the option of cryopreservation of gametes prior to initiation of therapy.

Animal data also indicate that vismodegib may irreversibly impair fertility. In rats, the number of corpora lutea and the number of motile sperms were affected. Therefore, as a precaution, sperm cryopreservation should be performed prior to initiation of therapy (SPC Erivedge®).

### Rituximab (MabThera®)

Rituximab is a genetically engineered monoclonal chimeric (mouse / human) anti-CD20 antibody (IgG1) causing B cell depletion. Primarily approved for the treatment of non-Hodgkin's lymphoma and rheumatoid arthritis refractory to standard therapy, rituximab is also used in cutaneous B-cell lymphomas and severe cases of vasculitis such as Wegener's granulomatosis.

Negative effects of rituximab on fertility have not been observed. Animal studies in monkeys showed no deleterious effects on reproductive organs. There are eight case reports in the literature of men who were on rituximab at the time of conception. Seven of the eight pregnancies resulted in the birth of healthy children; in one case, there was a spontaneous abortion [1].

Just like any IgG, rituximab crosses the placental barrier. Case reports and registry data include 200 pregnancies during therapy with MabThera®. If the mother received rituximab at the time of conception or early in the first trimester, no damage to the offspring was observed. Children whose mothers were on rituximab during the 2nd and 3rd trimester of pregnancy experienced transient B cell depletion and lymphocytopenia [2]. Therefore, rituximab should only be used in pregnant women when potential benefits outweigh the potential risks. Due to the long retention time of rituximab in patients with B cell depletion, the SPC for MabThera® recommends effective contraception in women of childbearing age during therapy and within twelve months after the end of treatment.

The use of rituximab in couples wishing to conceive and early in the first trimester currently appears to be feasible despite limited data. Administration in the second and third trimester causes substantial immunosuppression in the child. Breastfeeding is contraindicated.

Similar to maternal IgGs, rituximab is likely excreted into breast milk. This has already been demonstrated in monkeys. Therefore, women should not breastfeed during rituximab therapy as well as in the period of twelve months after the [last] administration [2].

  | JDDG | 1610-0379/2015/1304

## Allergology/Autoimmunity

### Omalizumab (Xolair®)

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody. In Germany, the drug has been approved for moderate to severe allergic bronchial asthma since 2005. In March 2014, it received additional approval for the treatment of chronic spontaneous urticaria (not adequately responding to H1 blockers).

There is no data on the effects of omalizumab on human fertility. In preclinical studies in monkeys, in which the antibody shows comparable IgE affinity, no effects on male and female fertility were found according to the SPC for Xolair®, not even after repeated overdosesing (up to 5-fold). Omalizumab is not genotoxic.

There is only limited experience as to the use of omalizumab in pregnant women. Omalizumab crosses the placental barrier. The internal registry of the manufacturer Novartis currently lists 300 uncomplicated pregnancies in asthmatics on Xolair®. Nevertheless, omalizumab should only be used during pregnancy, if it is absolutely necessary. No clinical data is available with respect to breastfeeding. According to the SPC, omalizumab should not be given to breastfeeding women. In monkeys, omalizumab levels in the milk are 1.5 % of maternal blood levels. No negative effects have been observed in the offspring.

Omalizumab likely does not impair fertility. In asthmatics, results have been very good regarding its use during pregnancy, whereas available data is limited with respect to breastfeeding.

### Anakinra (Kineret®)

Anakinra is a human recombinant interleukin-1 receptor antagonist. Approved for combination treatment of rheumatoid arthritis as well as cryopyrin-associated periodic syndromes (CAPS) such as Muckle-Wells syndrome, this substance shows impressive effects in rare autoinflammatory disorders such as Schnitzler syndrome. It has also been reported to be effective in pyoderma gangrenosum, Sweet's syndrome, SAPHO syndrome, and others.

The selective blockade of the IL-1 receptor by anakinra does not seem to negatively affect male fertility. On the contrary, in Muckle-Wells syndrome, which is sometimes associated with male subfertility, spermiogram parameters partly improved during treatment [16]. This is also in keeping with animal data that showed no effects on fertility, early development, development of the embryo/fetus, or peri- and postnatal development at extremely high doses. Anakinra is neither mutagenic nor genotoxic (SPC Kineret®).

However, there have only been three documented human pregnancies during anakinra therapy; all three were unremarkable [2]. Therefore, the use during pregnancy and in women of childbearing age not using contraception is currently not recommended. Passage of the active ingredient into human breast milk is likely, but has not been investigated. Therefore, according to the SPC for Kineret®, women should not breastfeed during treatment.

Anakinra does not affect fertility. The use in pregnancy and lactation is not recommended due to limited data. First reports, however, did not show any adverse effects.

### Summary

Owing to their high specificity, novel agents, including systemic biologics, show impressive therapeutic results. However, their use in couples trying to conceive and during pregnancy and lactation remains difficult due to limited data available. Following careful consideration of risks and benefits and obtaining the patient's informed consent, these agents then have to be used off-label (Table 4).

 

**Table 4** Summary of recommendations on the use of new systemic dermatologic agents in patients wishing to conceive as well as during pregnancy and lactation.

| | Fertility Man | Intake at conception (♂) | Fertility Woman | Intake at conception (♀) | Pregnancy | Lactation |
|---|---|---|---|---|---|---|
| *Psoriasis* | | | | | | |
| **Infliximab** | Unimpaired | Possible* | Unimpaired | Possible* | In the first trimester possible*, thereafter only after careful risk/benefit analysis | Possible* |
| **Adalimumab** | Unimpaired | Possible* | Unimpaired | Possible* | In the first trimester possible*, thereafter only after careful risk/benefit analysis | Possible* |
| **Etanercept** | Unimpaired | Possible* | Unimpaired | Possible* | In the firs trimester possible*, thereafter only after careful risk/benefit analysis; compared to infliximab and adalimumab significantly less pronounced passage into the fetal circulation | Possible* |
| **Ustekinumab** | Probably unimpaired | Not studied | Probably unimpaired | Not studied | Not recommended due to very limited data | Only after careful risk/benefit analysis |
| *Dermatologic oncology* | | | | | | |
| **Vemurafenib** | Not sufficiently studied | Not studied | Not sufficiently studied | Not studied | Only if the mother's life is at risk | Not studied, contraindicated |
| **Dabrafenib** | Impaired | Not studied | Impaired | Not studied | Only if the mother's life is at risk | Not studied, contraindicated |
| **Ipilimumab** | Possible impairment | Not studied | Impairment possible | Not recommended, increased risk of miscarriages | Only after careful risk/benefit analysis | Not studied |
| **Imatinib** | Impaired | Increased risk of miscarriages and malformations | Not sufficiently studied | Increased risk of abortion and malformations | Increased risk of miscarriages and malformations, only after careful risk/benefit analysis | Contraindicated, weaning is advisable |
| **Vismodegib** | Impaired | Contraindicated | Impaired | Contraindicated | Contraindicated | Contraindicated |
| **Rituximab** | Probably unimpaired | Possible | Probably unimpaired | Not recommended due to limited experience | In the first trimester possible*, thereafter only after careful risk/benefit analysis | Not studied, weaning is advisable |

*Continued*


 

Table 4 *Continued.*

| | Fertility Man | Intake at conception (♂) | Fertility Woman | Intake at conception (♀) | Pregnancy | Lactation |
|---|---|---|---|---|---|---|
| *Allergology* | | | | | | |
| **Omalizumab** | Probably unimpaired | Possible | Probably unimpaired | Only after risk/benefit analysis | Only after risk/benefit analysis | Probably safe, but not sufficiently studied |
| **Anakinra** | Probably unimpaired | Possible | Probably unimpaired | Only after risk/benefit analysis | Only after risk/benefit analysis | Probably safe, but not sufficiently studied |

*Recommendation by the Center for Pharmacovigilance and Consultation on Embryonal Toxicology at Charité Berlin (https://www.embryotox.de), considering current study data, in contrast to the Summary of Product Characteristics.

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# Questions for certification by DDG

**1. Which of the following definitions is incorrect?**

a) Genotoxic: Induction of DNA changes in vitro
b) Mutagenic: Induction of mutations/ chromosomal aberrations
c) Teratogenic: Induction of malformations in the embryo
d) Fetotoxic: Damage to the 'baby' before the embryonal stage
e) Reproductive toxicity: Impairment of fertility and/or damage to the unborn child

**2. Which of the following is not intended for fertility protection?**

a) Cryopreservation of gametes before the start of therapy
b) Cryopreservation of stem cells before the start of therapy
c) The use of a medication without toxic effects for reproduction
d) Avoidance of therapy
e) The start of therapy only after the couple no longer wishes to have children

**3. Which of the following sources does not offer medical doctors any information on the administration of medication in couples wishing to conceive and during pregnancy and lactation?**

a) The Red list
b) The Pink list
c) Summary of Product Characteristics (SPC)
d) Pharmacovigilance and Consultation Center for Reproductive Toxicology at the Charité
e) Literature search (PubMed)

**4. Which of the following statements about biologics for psoriasis in pregnancy is incorrect?**

a) There is an active transport of monoclonal antibodies against TNFα through the placenta into the fetal circulation.
b) Serum levels of infliximab and adalimumab in late pregnancy are significantly higher in the unborn child than in the mother
c) The active transport of etanercept across the placenta into the fetal circulation is much less pronounced than that of infliximab and adalimumab.
d) The body of evidence on the administration of ustekinumab in pregnant women is less comprehensive that that of TNF alpha inhibitors.
e) Etanercept has teratogenic effects.

**5. In association with which of the following drugs can cryopreservation of sperm prior to therapy begin be avoided in men who still want to have children?**

a) Vismodegib
b) Dabrafenib
c) Etanercept
d) Glivec
e) Ipilimumab

**6. Which of the following drugs reduces the efficacy of oral contraceptives?**

a) Dabrafenib
b) Omalizumab
c) Infliximab
d) Anakinra
e) Vismodegib

**7. Which statement about therapy of metastatic malignant melanoma is correct?**

a) Dacarbazin does not impair fertility.
b) Vemurafenib can be classified as safe for use in pregnancy.
c) Dabrafenib is not mutagenic, but it is teratogenic.
d) Ipilimumab is mutagenic, but not teratogenic.
e) Dabrafenib and vemurafenib may be administered to breastfeeding mothers.

**8. Which of the following statement on ipilimumab is incorrect?**

a) Impairment of fertility is possible.
b) The active substance is mutagenic.
c) Autoimmune hypophysitis secondary to CTLA4 blockade typically begins 4–6 months after initiation of therapy.
d) High-dose glucocorticoids are indicated for the treatment of autoimmune hypophysitis.
e) There is no clinical experience with the use during pregnancy and lactation.

**9. Which one of the following statements about therapy with rituximab is incorrect?**

a) Just as any IgG, rituximab crosses the placenta.
b) To date, no damage has been observed in children whose mothers received rituximab in the first trimester.
c) Administration of rituximab in late pregnancy is expected to lead to transient B-cell depletion and lymphocytopenia in the child.
d) Rituximab does not impair fertility.
e) Rituximab is not excreted into human breast milk.

**10. Which one of the following statements about omalizumab is correct?**

a) Omalizumab is a monoclonal antibody against IgG1.
b) Omalizumab is teratogenic.
c) Omalizumab does not cross placenta.
d) There are data on > 300 pregnancies without complications associated with therapy with omalizumab.
e) There is a large body of evidence on the use of omalizumab during breastfeeding.

Liebe Leserinnen und Leser,
der Einsendeschluss an die DDA für diese Ausgabe ist der 18. May 2015. Die richtige Lösung zum Thema „Photoallergy" in Heft 1 (January 2015) ist: (1a, 2d, 3c, 4d, 5e, 6c, 7a, 8c, 9e, 10b).

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