Interview

Betaferon® and Pregnancy
Issue 7/2019

INTERVIEW WITH PROF. DR. JELENA DRULOVIC

Registry data, the recently updated European Betaferon® label and what it means in clinical practice

Find out more in the interview with Prof. Dr. Jelena Drulovic inside this issue.

EDITORIAL

Many multiple sclerosis (MS) patients are women of childbearing age. Therefore, pregnancy is a major concern for many MS patients and they expect proactive counseling from their neurologist before, during and after the pregnancy.

In this series of articles we present the viewpoints of MS experts from around the world on the practical management of pregnancy and pregnancy-related topics for patients with MS. In this issue, Professor Jelena Drulovic from Belgrad University and Head of the largest academic MS center in Serbia gives us insights into the newly formulated section on pregnancy and breast-feeding in the European Betaferon® label and what the label text means in terms of patient management.

Patrick Salonis
Bayer U.S. LLC,
Global and US Brand Director, Betaferon®

More interviews to be published soon!

Interview with Prof. Dr. Jelena Drulovic

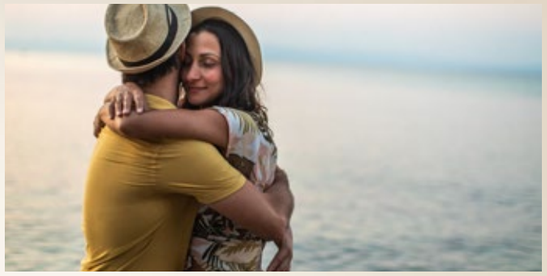
Registry data, the recently updated European Betaferon® label and what it means in clinical practice

Many MS patients these days are treated with a disease-modifying therapy (DMT) to control their disease. What is your experience with DMT exposure before pregnancy or during pregnancy?

Our experience is mainly based on interferon beta and glatiramer acetate exposure. In accordance with published data, with Neurology society guidelines and with European Summary of Product Characteristics for Interferon-ß (IFN-ß) therapies as recently updated, we advise patients on these therapies to continue treatment until pregnancy is confirmed and usually to stop it then. In our experience this is clinically a valuable approach. Once pregnant, a patient generally experiences a normal pregnancy with no particular features. Usually, pregnancy has a protective effect on the disease which may be increasing over the course of the 9 months. However, in some clinical instances it might be discussed with the patient whether it is advisable to continue IFN-ß therapy beyond pregnancy start. As regards other classes of therapies, our experience is limited to few pregnancies, mainly on monoclonal antibodies and we follow the drug label recommendations, which is for the majority of agents for the woman to stop when she plans to become pregnant.

There is data available from pregnancy registries about Betaferon® therapy. What do these datasets show and how do they impact the way you are counselling your patients regarding pregnancy planning?

Different registry studies have reported on pregnancies of women who conceived while taking Betaferon® or another IFN-ß formulation, and found rates of adverse pregnancy outcomes comparable with general population rates.[1,2,3,4] Two of these studies were mandated by the European Medicines Agency (EMA): a European IFN-ß



pregnancy registry with pharmacovigilance data from all four companies and a register-based cohort study on women with MS in Finland and Sweden.[3,4] The Nordic countries are well-known for their population-based national health registries, and this study allowed a direct comparison of pregnancies with IFN-ß exposure and pregnancies without exposure: 797 pregnancies exposed to only IFN-ß did not show an increase of serious adverse pregnancy outcomes including congenital anomalies or of spontaneous abortions versus 1,647 pregnancies not exposed to any MS medication.[4] Further outcomes included information on birth weight, birth height, and head circumference of the newborns with no statistical differences between groups.[5,6] In these published registries,[1–6] IFN-ß treatment was in most instances stopped after a positive pregnancy test. Accordingly, most of the reported data on pregnant women were from exposure before conception or during the first trimester of pregnancy. The findings of the EMA mandated IFN-ß pregnancy studies are now part of the aforementioned recently

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In your experience, how do IFN-ß-exposed pregnancies proceed when comparing to pregnancies that were not exposed to any DMT? Is there anything specific one has to consider?

I have not seen anything particular in my pregnant MS patients who had been exposed to IFN-ß.
I think there is nothing specific that would need to be considered. My observations are in line with the scientific data from registries and pharmacovigilance databases providing no indication of risks increased beyond the general risks of pregnancy.

Any final thoughts on the pregnancy, breast-feeding and Betaferon® you would like to share?

As said, we generally advise our patients to continue on Betaferon® until pregnancy is confirmed and then to stop. However, in some active cases, the continuation of Betaferon® throughout pregnancy may be clinically indicated (e.g. in cases with high likelihood of disease reactivation). In our academic center we closely follow up on these patients. We notice that such an approach can, in active cases, provide additional support to the patient, releasing her from the fear of not being protected by a DMT during pregnancy. One final remark on the updated EU Betaferon® label: So far women had to decide between breast-feeding and resuming Betaferon® treatment after delivery. Often pre-pregnancy disease activity guided the decision. Now the woman can postpartum also choose to both breast-feed and resume IFN-ß therapy; this is an important additional option for a mother with MS.

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PROF. DR JELENA DRULOVIC

Jelena Drulovic (born Nikolic), is full Professor of Neurology at the Faculty of Medicine University of Belgrade, and Head of the MS center, at the Clinic of Neurology, Clinical Center of Serbia, in Belgrade, Serbia.

Dr Drulovic graduated from Faculty of Medicine University of Belgrade in 1983. In 1986, she began to work as a resident at the Clinic of Neurology, Clinical Center of Serbia, Belgrade, Serbia. Following residency, she trained in neuropsychiatry at the Faculty of Medicine University of Belgrade, and passed the specialty exam in 1991. Since 1993, Dr Drulovic is involved in teaching neurology of medical students at the Faculty of Medicine University of Belgrade.
From 1999 to 2010, she was Head of the Unit of Neuroimmunology, at the Clinic of Neurology, Clinical Center of Serbia and from 2010 on Head of the MS Centre, at the Clinic of Neurology. From 2014, she is the president of the Multiple Sclerosis Task force of the Serbian Society of Neurologists. From 2018, she is the president of the Neurological advisory board of the Ministry of Health Republic of Serbia. Her main field of research interest is neuroimmunology and multiple sclerosis. Prof. Drulovic is a member of EAN Subspecialty Scientific Panel Multiple Sclerosis and EAN Subspecialty Scientific Panel on Neuroimmunology. Dr Drulovic has 132 publications in JCR list, out of more than 300 publications in international and national scientific journals. From 2009, she serves as Associate Editor of BMC Neurology.

[1] Amato et al. Neurology. 2010;75:1794-1802. [2] Thiel et al. Mult Scler. 2016;22:801-809. [3] Hellwig et al. AAN 2018, Poster P357. [4] Hellwig et al, AAN 2019, S 49.005.
[5] Burkill et al, ICPE 2019, Poster 766. [6] Vattulainen et al ECTRIMS 2019, P 1144.

Bayer AG

Betaferon®
(Refer to full SmPC before prescribing.)

Composition: *Active ingredient:* Recombinant interferon beta-1b 250 microgram (8.0 million IU) per ml when reconstituted. Betaferon contains 300 microgram (9.6 million IU) of recombinant interferon beta-1b per vial. *Excipients:* Human albumin, Mannitol. **Indications:** Betaferon is indicated for the treatment of patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite MS, patients with relapsing-remitting MS and two or more relapses within the last two years and patients with secondary progressive MS with active disease, evidenced by relapses. **Contraindications:** Patients with a history of hypersensitivity to natural or recombinant interferon beta, human albumin or any of the excipients. Patients with current severe depression and/or suicidal ideation. Patients with decompensated liver disease. **Special warnings / Precautions:** The administration of cytokines to patients with a pre-existing monoclonal gammopathy has been associated with the development of systemic capillary leak syndrome with shock-like symptoms and fatal outcome. • In rare cases, pancreatitis was observed with Betaferon use, often associated with hypertriglyceridaemia. • Betaferon should be administered with caution to patients with previous or current depressive disorders, in particular to those with antecedents of suicidal ideation. Patients should be advised to immediately report symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Betaferon and treated appropriately. Cessation of therapy with Betaferon should be considered. Betaferon should be administered with caution to patients with a history of seizures, particularly if their epilepsy is not adequately controlled with anti-epileptics. This product contains human albumin and hence carries the risk for transmission of viral diseases. A risk for transmission of Creutzfeld-Jacob disease cannot be excluded. • Thyroid function tests are recommended regularly in patients with a history of thyroid dysfunction or as clinically indicated. Complete blood and differential white blood cell counts, platelet counts, and blood chemistries, including liver function tests (e.g. AST (SGOT), ALT (SGPT) and γ-GT), are recommended prior to initiation and at regular intervals during Betaferon therapy. Patients with anaemia, thrombocytopenia and/ or leukopenia may require more intensive monitoring. • Severe hepatic injury, including cases of hepatic failure, has been reported rarely in patients taking Betaferon. The most serious events often occurred in patients exposed to other drugs or substances associated with hepatotoxicity or with comorbidity. Patients should be monitored for signs of hepatic injury. Withdrawal of Betaferon should be considered if serum transaminases levels increase significantly or are associated with clinical symptoms. • Caution should be used and close monitoring considered with severe renal failure. • Cases of nephrotic syndrome with different underlying nephropathies including collapsing focal segmental glomerulosclerosis, minimal change disease, membranoproliferative glomerulonephritis and membranous glomerulopathy have been reported, at various time points, during treatment with interferon-beta products and may occur after several years of treatment. Periodic monitoring of early symptoms and prompt treatment is required; and discontinuation of treatment with Betaferon should be considered, especially in patients at higher risk of renal disease. ♦Caution is required in patients with pre-existing cardiac disorders. Patients with pre-existing significant cardiac disease should be monitored for worsening of their cardiac condition, particularly during initiation of treatment with Betaferon. While Betaferon does not have known direct-acting cardiotoxicity, flu-like symptoms may prove stressful to pre-existing heart disease. Rare cases of cardiomyopathy have been reported: If this occurs and a relationship to Betaferon is suspected, treatment should be discontinued. • Cases of thrombotic microangiopathy (TMA), manifested as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome have been reported with interferon-beta products. Events were reported at various time points during treatment and may occur several weeks to several years after starting treatment with interferon-beta. If TMA is diagnosed, prompt treatment is required and immediate discontinuation of Betaferon is recommended.
• Serious hypersensitivity reactions may occur. If reactions are severe, Betaferon should be discontinued and appropriate medical intervention instituted. • Injection site necrosis has been reported in patients using Betaferon. It can be extensive and may result in scar formation. If the patient experiences any break in the skin, the patient should be advised to consult with his/her physician before continuing Betaferon injections. If the patient has multiple lesions Betaferon should be discontinued until healing. **Undesirable effects:** At the beginning of treatment adverse reactions are common but in general they subside with further treatment. The most frequently observed adverse reactions are a flu-like symptom complex and injection site reactions. Dose titration is recommended at the start of treatment in order to increase tolerability to Betaferon. Flu-like symptoms may be reduced by administration of non-steroidal anti-inflammatory drugs. The incidence of injection site reactions may be reduced by the use of an autoinjector. **Undesirable effects which were significantly associated with Betaferon treatment in clinical trials:** *Very common:* lymphocyte count decreased, absolute neutrophil count decreased, white blood cell count decreased, headache, abdominal pain, alanine aminotransferase increased, rash, hypertonia, myalgia, injection site reaction, flu-like symptoms, fever, asthenia, chills; *Common:* abnormal vision, palpitation, hypertension, dyspnoea, vomiting, aspartate aminotransferase increased, menstrual disorder, injection site necrosis, chest pain, sweating, malaise. **Undesirable effects identified during post-marketing surveillance:** *Very common:* arthralgia; *Common:* anaemia, hypothyroidism, blood bilirubin increased, weight increased, weight decreased, confusional state, tachycardia, urticaria, pruritus, alopecia, menorrhagia; *Uncommon:* thrombocytopenia, blood triglycerides increased, suicide attempt, emotional lability, convulsion, hepatitis, skin discolouration, nephrotic syndrome, glomerulosclerosis; *Rare:* thrombotic microangiopathy including thrombotic thrombocytopenic purpura/ haemolytic uraemic syndrome, anaphylactic reactions, hyperthyroidism, thyroid disorders, anorexia, cardiomyopathy, bronchospasm, pancreatitis, hepatic injury, hepatic failure. *Frequency not known:* capillary leak syndrome in pre-existing monoclonal gammopathy, drug-induced lupus erythematosus, pulmonary arterial hypertension.

Please refer to the Summary of Product Characteristics for further information.
On prescription only.
Marketing Authorisation Holder: Bayer AG, 51368 Leverkusen, Germany.
Date of issue of Marketing Authorisation valid throughout the EU: 30.11.1995.
Date of last Renewal: 31.1.2006. **Date of last SmPC revision:** 19.09.2019

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