Interview

Betaferon® and Pregnancy
Issue 5/2019

INTERVIEW WITH DR. GIROLAMA ALESSANDRA MARFIA

MS, pregnancy and breast-feeding counseling in the treatment era

Find out more in the interview with
Dr. Girolama Alessandra Marfia inside this issue.

EDITORIAL

The typical multiple sclerosis (MS) patient is a woman 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 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, Dr. Girolama Alessandra Marfia from Italy, focuses on counseling and recommendations for patients who want to become pregnant or who ask whether they should breast-feed or not. She also summarizes the results of pregnancies exposed to interferon beta (IFN-ß) being comparable with those of the general population. Moreover, she refers to the newly updated text of the pregnancy and breast-feeding label of IFN-ß therapies, like Betaferon®.

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

More interviews to be published soon!

Interview with Dr. Girolama Alessandra Marfia

MS pregnancy and breast-feeding counseling in the treatment era

Dr. Marfia, these days, MS pregnancy counseling is complicated by the availability of numerous treatment options for MS. Could you please summarize the main aspects a neurologist should consider when counseling a patient on MS therapy related to pregnancy?

Treatment considerations should be evaluated at every single stage of the perinatal journey.

The management of DMT (disease-modifying therapies) in MS patients planning to become mother involves pre-pregnancy, pregnancy and post-pregnancy tailored considerations. Potential risks associated with all therapies should be carefully balanced against the expected benefit in individual patients. Neurologists should evaluate the possible teratogenic risk for the foetus derived from the exposure in utero to the drug against the possibility

of relapse and disability progression in the mother due to drug discontinuation. Most DMTs are contraindicated during pregnancy and most women are advised to stop using them before conception; physicians may have to consider risk versus benefit when deciding to discontinue treatment. This individualized combined risk should be carefully balanced on the basis of the mother's disease characteristics and the available evidence in terms of safety profile of the medications. Drugs such as interferon beta (IFN-ß) and glatiramer acetate have a long history of use at conception and safety data on pregnancy have been collected and have not shown an increase in adverse pregnancy outcomes. On the other hand, the majority of emerging infusion and oral therapies still have limited pregnancy data. The choice of the most appropriate strategy for the individual patient should be grounded on available scientific evidence-based data and shared clinical experience.

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In your clinical practice, what's the advice to a patient taking Betaferon and wanting to become pregnant with regard to stopping the medication? Please explain the aspects that lead to your advice.

Physicians who treat MS patients that wish to conceive have to consider the large prospective datasets showing that IFN-ß exposure during pregnancy is not associated with adverse outcomes. Based on this evidence, IFN-ß has been recently re-evaluated by the European Medical Agency. In turn, the re-evaluation has led to a label update that removes both the 'pregnancy initiation' contraindication as well as the mandate that women taking IFN-ß need to take contraception measures. The pregnancy section of the IFN-ß labels refers to a large amount of data (>1,000 pregnancies) indicating no increased risk of congenital anomalies in association with IFN-ß exposure before conception or during the first trimester of pregnancy. Therefore, therapy with IFN-ß does not need to be discontinued in women with MS when planning a pregnancy.

There is a considerable amount of data available from patients who have continued an IFN-ß therapy until pregnancy. The newly updated text of the pregnancy label refers to this data. What is most important about these data? And what are their clinical implications?

These data are collected in the study presented as a poster at ECTRIMS 2018 which examined pregnancies during treatment with Betaferon®.[1] The results covered 1348 prospective pregnancies with exposure to Betaferon® mainly limited to the first trimester collected from the Bayer Pharmacovigilance database. The majority of the pregnancies recorded were normal, resulting in healthy babies. Pregnancies exposed to Betaferon® were not associated with an increased risk of congenital anomalies when compared with the general population. No specific pattern of birth defects were seen.[2]
The Nordic cohort study used health care register data from Sweden and Finland (2005–2014) to study women with MS.[3] Women were included if they were diagnosed with MS and had a pregnancy with a recorded outcome during the study period. The Nordic study, in addition to other outcomes, gave no evidence that exposure to IFN-ß during pregnancy influenced birth weight, birth length or head circumference.[4] The Nordic register outcomes were also consistent with the results of the European IFN-ß Pregnancy Registry.[5] Both studies did not show any evidence that IFN-ß exposure before conception and/or during pregnancy adversely affected pregnancy or infant outcomes.[3–5]
These data should make clinicians feel more confident in counseling women with MS to continue Betaferon® until the confirmation of pregnancy. This has an important implication as patients can continue to benefit from a reduced risk of a relapse during their attempt to conceive.

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What are your recommendations to patients who ask whether they should breast-feed or not? And what drives this recommendation?

In the majority of studies, breast-feeding has no impact on MS relapses, although a few studies suggest a potential protective role. Because DMTs may enter breast milk, they are normally withheld during breast-feeding. The decision to resume DMT treatment immediately after birth needs to be weighed against the potential benefits of breast-feeding for the child. The decision whether or not to breast-feed depends on several factors: first of all patient's decision that should be balanced with the individual profile of risk. In general, probability of postpartum relapse is higher in women with active disease in the year preceeding pregnancy. Moreover, patients with highly active disease should be discouraged from breast-feeding and an early resumption of DMT after delivery should be proposed. In our clinical practice, we promote a standardised monitoring that includes MRI scan 30–40 days after birth to re-baseline disease activity and to re-discuss breast-feeding options on an individualised basis and to plan future shared decision about DMT resumption. This might be different for MS patients using IFN-ß. Even though there are only limited information available on the transfer of IFN-ß into breast milk, the transfer in human milk is suggested to be negligible due to the chemical/physiological characteristics of IFN-ß, e.g. its molecular weight. Moreover the drug is not orally bioavailable so that it might not reach the child blood circulation even if traces would appear in the breast milk. According to the new European SmPC (Summary of Product Characteristics) for IFN-ß no harmful effects on the breast-fed newborn/infant are anticipated and IFN-ß, like Betaferon®, can be used during breast-feeding.

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Any final thoughts on this topic you would like to share?

The fact that pregnancy rates have been increasing over the past 10 years in women with MS is extraordinary; this implies our increasing understanding of pathogenic mechanisms resulting in successful treatment and management of the disease in general. All these factors on the whole result in more women – independently from having received such a diagnosis – feel free to plan family, social and job opportunities like their healthy peers.
I believe in the development of appropriate and proactive family planning counseling in MS centers worldwide. An interdisciplinary approach is essential and would help in providing reassurance to patients that pregnancy is feasible with appropriately tailored management practices.

“I believe in the development of appropriate and proactive family planning counseling in MS centers worldwide. An interdisciplinary approach is essential and would help in providing reassurance to patients that pregnancy is feasible with appropriately tailored management practices.”

DR. GIROLAMA ALESSANDRA MARFIA

Dr. Girolama Alessandra Marfia is an Assistant Professor of Neurology in the Clinic of Neurology, System Medicine Department, University of Rome “Tor Vergata”, Italy and is the Head of the MS Unit of the Tor Vergata University Hospital in Rome, Italy.

Her scientific interest and research concern the complex relationship between clinical, radiological, neurophysiological and CSF biomarkers of neuroinflammation and neurodegeneration in MS. She is the Principal Investigator of many phase II, III and IV national and international trials with new therapeutic agents for MS conducted according to Good Clinical Practice (GCP). Dr. Marfia clinical and research interests extend also to acute and chronic inflammatory neuropathies and neuropathic pain. A very important focus of Dr. Marfia is in the area of MS and pregnancy. In May 2016 she started the MS Pregnancy Unit, a special project focused on pregnancy in women with MS, in her MS Centre at Tor Vergata University Hospital in Rome. Dr. Marfia is author of about 80 peer-reviewed papers published in international journals of neuroscience and neurology.

[1] Hellwig K et al., Poster P1771, ECTRIMS 2018, Berlin (Germany).
[2] Hellwig K et al., Poster 2.101, AAN 2019, Philadelphia (USA).
[3] Hellwig K et al., S 49.005, AAN 2019, Philadelphia (USA).
[4] Burkill S et al., Poster 766, ICPE 2019, Philadelphia (USA).
[5] Hellwig K et al., Poster P4.357; AAN 2018, Los Angeles (USA).

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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