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Immunomodulating Treatment of Multiple Sclerosis — the Tasks and Role of a Neurological Nurse

Immunomodulacyjne leczenie stwardnienia rozsianego — zadania i rola pielęgniarki neurologicznej

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Abstract

Multiple Sclerosis (SM) is the most common chronic inflammatory autoimmune demyelinating disease affecting the central nervous system. It affects mainly young people, aged 20–40.The onset of the disease usually takes the form or bouts followed by periods of remission. Immunomodulating treatment is a long-term therapy whose aim is to inhibit the occurrence of relapses and, in the long term-delay development of disability in a patient. The effectiveness of this treatment depends, among others, on the degree of preparation of the patient and their following the rules of the therapy. Most of the medication applied is administered by the patient at home as an injection or in the form of oral therapy. Nowadays two drugs are administered in hospitals. Since the very beginning of the treatment the patient and their family is provided with nursing care whose scope depends on the drug administered and on the condition of a patient. The procedures undertaken by the nurse include: educating the patient and their family in the preparation and administration of a drug, coping with adverse effects, monitoring the neurological and emotional condition of a patient and providing support during all treatment period. **(JNNN 2018;7(4):160–165)**
Key Words: multiple sclerosis, immunomodulating drugs, nursing care

Streszczenie

Stwardnienie rozsiane jest przewlekłą, demielinizacyjną chorobą ośrodkowego układu nerwowego o podłożu immunologicznym. Dotyczy głównie ludzi młodych, pomiędzy 20., a 40. rokiem życia. Początek choroby występuje najczęściej pod postacią rzutów i następujących po nich okresach remisji. Leczenie immunomodulacyjne jest terapią długotrwałą i ma na celu zahamowanie występowania rzutów choroby, a w dalszej perspektywie opóźnienie wystąpienia niesprawności u chorego. Skuteczność tego leczenia zależy m.in. od stopnia przygotowania pacjenta i przestrzegania przez niego zasad terapii. Większość stosowanych leków pacjent przyjmuje samodzielnie w warunkach domowych, pod postacią iniekcji lub doustnie. Obecnie dwa preparaty podawane są w warunkach szpitalnych. Od początku leczenia chory i jego rodzina zostają objęci opieką pielęgniarską, która jest zróżnicowana w zależności od zastosowanego preparatu oraz stanu klinicznego chorego. Działania podejmowane przez pielęgniarkę obejmują m.in.: edukację chorego i jego rodziny w zakresie umiejętności samodzielnego przygotowywania i podawania leku, radzenia sobie z działaniami niepożądanymi, monitorowanie stanu neurologicznego i emocjonalnego pacjenta oraz udzielanie wsparcia przez cały okres leczenia. **(PNN 2018;7(4):160–165)**
Słowa kluczowe: stwardnienie rozsiane, leki immunomodulacyjne, opieka pielęgniarska

Introduction

Multiple Sclerosis (SM) is the most common chronic inflammatory autoimmune demyelinating disease affecting the central nervous system. It is also the most common cause of permanent disability among young people. Despite identifying the factors influencing the course of the disease, complete etiology of the condition

has not been fully discovered. The main concept of occurrence of SM is based on the autoimmune theory [1]. Patients experience abnormal immunological reaction because of disturbed functioning of immune system or its abnormal reaction to an infectious agent. The disease is most often diagnosed in adults between 20 and 40 years old. Compared to men, women are twice as likely to develop SM [2].

In the progression of multiple sclerosis, depending on the different clinical course, four basic types of the disease.

1. Relapsing-Remitting Multiple Sclerosis (RRMS) — the disease takes the from of relapses — exacerbation of already present symptoms or new neurological deficits, followed by partial or complete remission.
2. Secondary Progressive Multiple Sclerosis (SPMS) — characterized by steady progress of neurological symptoms without specific relapses, which gradually leads to a permanent disability.
3. Progressive Multiple Sclerosis (PPMS) — which makes for 15–20% of cases, is characterized not by relapses but by steady worsening of neurological functioning without distinct relapses.
4. Progressive Relapsing Multiple Sclerosis (PRMS) — about 10% of cases. It takes the course of relapses along with gradual and significant progression of MS symptoms [3,4].

In about 80% of patients, multiple sclerosis takes the relapsing-remitting form. In the initial stage of the condition inflammatory process dominates over the neurological-degenerative process, thus administering immunomodulating drugs has a positive therapeutical effect [5]. The aim of the treatment at this stage is decreasing the number and severity of relapses, reducing radiation in magnetic resonance imaging, slowing the progress of disability (evaluated by EDSS scale) and improving the quality of life of a patient [5,6]. Nowadays immunomodulating therapies are available in Poland and refunded by the Polish NHS. The registered medications available in these programmes include: first line medications (interferons beta, glatiramer acetate, dimethyl fumarate, peginterferon β1a, teriflunomide) and second line medications (fingolimod and natalizumab). To receive medication a patient has to be qualified by a neurologist. The qualification to treatment is based on assessment including the duration of disease, number of relapses and the neurological condition between relapses (based on EDSS scale) [7].

Recommendations related to using immunomodulating therapy drugs change together with new research and development and registration of new drugs. They may also be different in particular countries. According to the treatment algorithm, treatment of the relapsing-remitting form of MS in Poland starts with first line medications, particularly in patient with low clinical and radiological activity of MS. The only exception is the aggressive form of the relapsing-remitting MS, where the treatment can be initiated with administering natalizumab and omitting the first line medications [6]. In case of ineffectiveness of a first line medication, second line drugs are used [5,6,8]. Ineffectiveness of the treatment is understood as: the lack of response to a full, at least a year-long cycle of treatment with at least one medication, experiencing at least one relapse by the patient and one or more intensifying changes after administering gadolinium contrast, or at least 9 T2-hyperintense foci. The definition also includes cases of experiencing the same or bigger number of relapses or experiencing more intensive relapses than in the previous year of the treatment [5,6].

Review

First Line Immunomodulating Medications:

a. Interferons

Among interferons we may distinguish interferon β1b and β1a. As the first one interferon β1b was registered in 1993 in the United States. Interferon β (IFN-β) is a natural cytokine, produced mainly by the immune system cells in response to viral infection. The exact way interferons work in multiple sclerosis has not been fully recognized. The main mechanisms consist in slowing the inflammatory process and T-cell proliferation, and limiting the movement of the inflammatory cells to CNS and reducing the number of them crossing the blood — brain barrier [9,10]. There are slight differences between interferon β1a and 1b in the way they are built (the length of amino acid sequence) and the way they are produced. The medications are administered in subcutaneous or intramuscular injection, according to the drug specification description (depending on the drug, it can be administered 3 times a week, every other day or once a week — intramuscular injections) [11]. Since 2017 peginterferon β1a has been available — used as a subcutaneous injection once or twice a week.

Nursing care of a patient receiving interferons

Nursing care is aimed mainly at preparing the patient for the therapy and minimizing the adverse effects of the treatment. Preparation for the treatment consists in educating the patient in preparing and administering the drug themselves. It is important to teach the patient particular stages of the procedure. It is necessary to pay special attention to the drug storage conditions (according to the summary of product characteristics), method of preparation of the drug, choosing the place of injection (stomach, arms, thigh, buttocks for the subcutaneous

injection; internal or frontal part of a thigh for intramuscular injection; avoiding places with skin alteration, painful, reddened or swollen), the method of administering the drug (the injection drugs are administered using special autoinjectors). It is recommended that already the first injection should be done by the patient themselves, which gives them a positive enhancement, helps to overcome reluctance that some patients experience before making the injection themselves. It is also important to emphasize that during all stages of administering the medications the rules of asepsis and antisepsis should be obeyed, according to the procedure. It is also important to show the patient how to behave in case of not being able to inject the medication right after dissolving it. In this case the medication should be put into a fridge and should be administered within the next 3 hours. After 3 hours it should be reprocessed and the next dosage should be prepared [12,13].

While providing the care, a nurse also teaches a patient how to deal with adverse effects of the drug. These include flu-like symptoms (raised body temperature, headache, muscle pain, shivering, sweating, feeling under the weather), symptoms connected with the place of injection (reddening, swelling, erythema, local infection) and depression. Patients should be informed that such flu-like symptoms are common in the beginning of the treatment and disappear as the therapy continues. These symptoms often appear 4–6 hours after administering the drug. Nurses recommend patients to take 2 pills of paracetamol before making an injection and taking the medication in the evening. To minimize the adverse effects connected with the place of injection, the patient should be advised to change the place of injection every time and to observe the skin after making the injection. It is recommended to apply a cooling gel pad after the injection. The skin reactions are more common with subcutaneous medications [14,15].

To improve monitoring of patients' following the procedure, they are asked to keep self-control diaries in which they note the date and place of administering the drug and any side effects that appear. Nurses also pay attention to the emotional condition of patients. Special attention should be paid if the following symptoms occur: crying, emotional lability, chronic sadness or dejection. If any worrying symptoms should occur, the doctor treating the patient should be informed. In such a case the doctor may decide to change the medication or to include antidepressant treatment. It is crucial for the patient to understand that following the recommendations described above is one of the most important factors influencing the effectiveness of the therapy [12–15].

b. Glatiramer acetate

Glatiramer acetate is a copolymer of four amino AIDS (L-glutamic acid, L-lysine, L-alanine and L-tyrosine) which in the way it is built resembles myelin basic protein. Its exact way of working has not been fully understood. It is believed that it affects T-cells activation and their proliferation. The available glatiramer acetate preparation is in subcutaneous dosage administered every day [16,17].

Nursing care of a patient receiving glatiramer acetate

Similarly as with inteferons, the nursing care is aimed at preparing the patient for the therapy and minimizing its side effects. Also with this medication the patient should be trained in the method of proper preparation and administering the drug (with autoinjector), according to the summary of product characteristics. The adverse effects of this copolymer are local skin alterations: swelling, reddening, inflammatory infiltration, subcutaneous tissue atrophy which may occur in long-term treatment. Following the recommended drug administration procedure by the patients reduces the occurrence of skin alterations. After the injection the place should be cooled with a gel pad. In about 15% of patients there is possibility of so-called systemic reaction (face blushing, heaviness in the chest, palpitation, breathlessness and fear). It is important for the patient to be aware that these symptoms will subside soon, they are present usually after administering the drug (from 30 seconds to 30 minutes) and they are not harmful for them [12–15].

c. Dimethyl fumarate

Dimethyl fumarate is the metyl ester of fumaric acid, used also in the treatment of psoriasis. Its therapeutic mechanism in MS in not completely understood. The preclinical trials indicate that the pharmacodynamic effect of dimethyl fumarate stems from the activation of the transcription factor (erythroid-derived 2)-like 2 (Nrf2) pathway. It was discovered that dimethyl fumarate causes a brief period of oxidative stress that results in the intraneuronal synthesis of the antioxidant glutathione (GSH) mediated through the Nrf2 pathway. In preclinical and clinical trials dimethyl fumarate showed anti-inflammatory and immunomodulating properties. Dimethyl fumarate strongly inhibited the activation of immunological system cells and production of proinflammatory cytokines in response to inflammatory stimuli [18].

Nursing care of a patient receiving dimethyl fumarate

The nurse educates patient receiving dimethyl fumarate in the method of administering the drug and its adverse effects. The initial dosage is 120 mg twice a day. After 7 days the dosage should be increased to the recommended 240 mg twice a day. The capsules should

be swallowed whole (shouldn't be chewed, crushed or dissolved as it can lead to intestine irritation). In case of omitting a dosage, no double dosage should be administered. The omitted dosage should be taken later, but 4 hours before the following dosage.

Adverse effects include: gastrointestinal events, flushing and headache. To reduce the occurrence of side effects it is recommended to take the medication with a food. While experiencing gastrointestinal events the patient may also use some drugs available without prescription, e.g. omeprazole or loperamide. The symptoms subside within a month of administering the medication [19,20].

d. Teriflunomide

It is an immunomodulating medication of anti-inflammatory properties which selectively and reversibly of inhibits activity the mitochondrial enzyme dihydroorotate dehydrogenase in the immunological system cells. The precise mechanism of its therapeutic effect is the treatment of MS is not fully understood, but may consist in the reduction of T and B lymphocytes [21,22].

Nursing care of a patient receiving teriflunomide

The nurse educates patient receiving in the method of administering the drug and its adverse effects. It is an oral drug in 14 mg dosage taken once a day. The food taken together with the medication does not effect its pharmacological properties. The most common adverse effects include: elevated alanine aminotransferase activity (AlAT), leukopenia and hypertension, thus these parameters should be monitored during treatment. Other side effects include: diarrhea, dizziness hair loss, headache, paresthesia, and infection of upper respiratory tract. These are usually mild symptoms which subside during the therapy [21].

Second Line Immunomodulating Medications:

a. Natalizumab

It is a humanized monoclonal antibody which binds to α4β1-integrin, found on the surface of lymphocytes and monocytes taking part in the processes of adhesion and cell transmigration. Natalizumab reduces the ability of lymphocytes to attach to and pass through blood-brain barrier, thus limiting the inflammation process within the CNS [23]. The medication was first registered for treating MS patients in 2004, after a year it was withdrawn to be reintroduced in 2006. Nowadays it is recommended in the treatment of patients with high disease activity, where treatment with interferons or glatiramer acetate has proven ineffective. Trials of natalizumab indicated its effectiveness in reducing the number of relapses, limiting the progress and radiological activity of the disease [24].

Nursing care of a patient receiving natalizumab

The tasks and role of a nurse include preparation and administration of the drug and monitoring the patient during all the period of therapy.

Natalizumab is administered by intravenous infusion of 300 mg every 28 days. The drug is in concentrated form and has to be dissolved in 100 ml of 9% sodium chloride. The solution is administered by intravenous infusion over one hour with the speed of 2ml/hour. To make sure the patient receives all the dosage it shouldn't be administered together with other medications. The solution which hasn't been used can be stored 2–8°C (36–46°) but must be infused within 8 hours. During the infusion and over an hour afterward the patient should be monitored for allergic reaction. The nurse measures blood pressure, pulse and temperature of a patient before the infusion, right after administering the drug and an hour afterwards. The most common adverse effects include headache, dizziness, nausea, urticaria and shivering [25].

The nurse monitoring a patient should pay attention to symptoms which may appear throughout all the period of treatment. These include: fatigue, fever, pain in the joints, urinary and respiratory tract infections [25]. A very rare but dangerous adverse effect of natalizumab is progressive multifocal leukoencephalopathy (PML), an opportunistic infection caused by the JC virus. It is characterized by the occurrence of symptoms of dementia, clumsiness, progressive weakness and visual changes, coma and possible death. The risks factors of developing PML include: period of treatment >2 years, previous use of immunosuppressive medication and presence of JVC antibodies in patient's serum. During qualification for the treatment a test for JVC antibodies should be done. A nurse looking after a patient receiving natalizumab should pay special attention to any disturbance of cognitive functions which may occur — as they are one of the symptoms of PML [26].

b. Fingolimod

It is a selective immunosuppressive drug, a sphingosine -1-phosphate receptor modulator (SP1). It binds with the SP1 receptors on the surface of lymphocytes and breaks through the blood-brain barrier to CNS. There it binds with the nerve cell receptor. By blocking the T and B lymphocytes from entering the lymph node, it also decreases the migration of cells to CNS, where they could take part in inflammatory process [27].

Nursing care of a patient receiving fingolimod

While preparing the patient for therapy a nurse should first present the rules of administering the

medication. It is administered orally in the form of 0.5 mg capsules once a day between meals or during meals. The first administration of the drug takes place in hospital — which is related to the possibility of cardiac dysrhythmia. After the first dosage, there may be a drop in blood pressure, with its lowest level at 6 hours after administering he medication. This is the reason why it is recommended to monitor the heart activity with an electrocardiogram (ECG) for the first 6 hours after administering fingolimod. Before the first dosage and every hour after monitoring blood pressure should be checked. The nurse is obliged to keep a record of the blood pressure and heart rate measurements every hour. After a month the heart activity is back to normal. The second and following dosages of the medicine are taken by the patient at home. It is crucial for the patient to understand the important of regular administration of the drug. A patient must not modify the dosage of the medicine either. In case of a break in taking the drug, patient should inform his doctor, as taking another dosage may require monitoring, just like with the first dosage. These issues have to be clearly discussed with the patient [28,29].

Before admitting the patient to the treatment it is necessary to inform them about possible adverse effects, such as: flu infection, herpesviruses, headaches, back pain, cough, depression, hypertension, gastrointestinal events (diarrhoea). A patient should observe whether these effects occur, and if worried — consult their doctor or nurse looking after them during the therapy [28,29].

Monitoring Treatment

In Poland monitoring patients receiving immunomodulating treatment is based on recommendations of the treatment programme prepared by the National Health Service. These include information about the types of diagnostic tests and their frequency for the patients admitted to the treatment. Their aim is to evaluate efficiency of the treatment and to allow further treatment in the programme. With the three medications described above, every three months, the patient has to undergo a neurological diagnosis with the EDSS scale assessment and lab tests (blood count, liver test). Every 6 months it is necessary to do a biochemical blood test and general urine test. Once a year a head MRI is done. With natalizumab additionally every 6 months a test for JVC antibodies is performed [7].

A difficult issue connected with the disease and immunomodulating treatment is planning pregnancy among women suffering from MS. Nowadays it is required that a woman admitted to the treatment should do a pregnancy test to make sure she is not pregnant. During treatment women should take contraceptives. It is connected with the teratogenic impact of the first and second line medication. There is no scientific evidence indicating harmful effects of the medication, however according to the summary of product characteristics, these medications are not recommended during pregnancy. Planning for motherhood during therapy is a difficult issue which is often discussed with SM patients. On the one hand, a break in therapy may result in relapses and progress of the disease, but on the other hand, women feel a great need of having a child. A nurse looking after the patient during treatment should also discuss these issues with patients, and present the knowledge about fertility and motherhood in a reliable way, based on recent research.

Conclusions

Multiple sclerosis is a chronic, progressive disease which may lead to disability. This is the reason why, in order to reduce its negative impact, it is important to start early immunomodulating treatment. The therapy is assumed to be systematic and long-term, requiring from the patient to obey established rules and to cooperate with their doctor and nurse. At every stage of the treatment patients face some problems and difficulties. It is the way a nurse leads the patient through the therapy that the success of the therapy is dependent on, and-as a consequence — so is preserving a better quality of life of a MS patient.

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