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Course of Care of a Multiple Sclerosis Patient in the Context of Pharmacotherapy

Przebieg opieki nad chorym ze stwardnieniem rozsianym w kontekście farmakoterapii

Anna Smelkowska[1,2], Maria Wilkiewicz[1], Barbara Grabowska-Fudala[1], Krystyna Jaracz[1]

[1]Department of Neurological and Psychiatric Nursing, University of Medical Sciences, Poznań, Poland
[2]Stroke Intensive Care Unit, Poznań, Poland

Abstract

Multiple sclerosis (SM) is an incurable, advancing, demyelinating illness with inflammatory background. It constitutes the most frequent cause of disability among young people, between 20 and 40 years of age. Despite the identification of multiple factors causing the disease, its pathomechanism has not been yet completely discovered. For this reason, finding an effective cure for multiple sclerosis continues to present a challenge (for modern scientists). The currently available treatment for SM aims to halt its progress and to minimalize complications related to the disease. The goal of the work was to provide an overview of the therapies currently available to those suffering from SM. Selecting an appropriate form of treatment and medication as well as preparing the patient and continuation of monitoring during the therapy constitute important elements of conducting an effective SM therapy. **(JNNN 2015;4(3):130–137)**
Key Words: multiple sclerosis, immunomodulatory therapy, monoclonal antibodies

Streszczenie

Stwardnienie rozsiane (SM) jest nieuleczalną, postępująca chorobą demielinizacyjną o podłożu zapalnym. Stanowi najczęstszą przyczynę niepełnosprawności wśród ludzi młodych, pomiędzy 20 a 40 rokiem życia. Pomimo identyfikacji licznych czynników wywołujących chorobę, jej patomechanizm wciąż nie został do końca poznany. Z tego względu opracowanie skutecznego leku na stwardnienie rozsiane wciąż stanowi wyzwanie dla współczesnych badaczy. Obecnie dostępne leczenie SM ma na celu zahamowanie jej postępu i minimalizację powikłań choroby. Wybór preparatu stosowanego w terapii chorych uzależniony jest od licznych czynników. Celem pracy było przedstawienie obecnie dostępnych metod terapii chorych na SM. Ważnym elementem prowadzenia skutecznej terapii chorych z SM jest nie tylko odpowiedni dobór formy leczenia i preparatu, ale również przygotowanie chorego i jego dalsze monitorowanie podczas trwania terapii. **(PNN 2015;4(3):130–137)**
Słowa kluczowe: stwardnienie rozsiane, leczenie immunomodulacyjne, przeciwciała monoklonalne

Introduction

Multiple Sclerosis (SM) is the most common chronic inflammatory autoimmune demyelinating disease affecting the central nervous system. Despite identifying the factors influencing the course of the disease, complete etiology of the condition has not been fully described. 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. Autoimmunization is explained by the similarity of the antigens of an infectious agent to body's own tissues. There are several pathogens whose antigens are similar to myelin proteins. To this group belong viruses: SFV E2, Epstein-Barr (EBV), flu viruses, HTLV-1, RSV. Also the infections with staphylococcal entertoxin, herpes virus (HHV-6) and measles virus can generate autoreactive T lymphocytes which attach myelin antigens. Autoreactive lymphocytes break the damaged blood-brain barrier to the central nervous system, where they initiate a complex process of intercellular response which leads to damage of meylin sheaths of axons (demyelination). In the pathogenesis of SM key role is played by lymphocytes helper

l. producing multiple proinflammatory cytokines and supporting cellular response, CD4+ lymphocytes (which produce proinflammatory cytokines, prostaglandins, CD8+ lymphocytes (are the main ingredients of inflammatory infiltration in actively demyelinating lesions, they also produce cytotoxic substances attacking oligodendrocytes and neurons), and also B lymphocytes (B cells). Among the dominating pathological processes apart from demyelination, there also occur damage and loss of oligodentrocytes, damage of axons, atrogliosis and loss of neurons [2-5].

Research in pathogenesis of multiple sclerosis indicates that a key role is also played by genetic factors which have an impact on susceptibility to the disease, type of course and severity of symptoms [6]. The disease is most common among people with white skin. There is also characteristic geographical distribution of the disease. Condition is more common in high-latitude areas, which is explained by the role of environmental factors in the pathogenesis of the disease [7]. These regions are characterized by decreased sunlight exposure, which results in decreased vitamin D production, which in turn affects immune system. This is why in Scandinavian countries, Great Britain, Canada and northern parts of the United States, there are several times more cases of the disease than in the Mediterranean countries [8]. Poland is a country with high risk of the disease, with prevalence of the disease of 40-80/ 100 000 of inhabitants. The disease is most often diagnosed in adults between 20 and 40 years old [9]. Compared to men, women are twice as likely to develop SM. Because of a progressive character of neurological disorders, SM is the most common cause of permanent disability among young people [10].

In the progression of multiple sclerosis, depending on the different clinical course, four basic phenotypes of the disease have been identified:

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. This is the most common disease course.

Secondary Progressive Multiple Sclerosis (SPMS) - characterized by steady progress of neurological symptoms without specific relapses, which gradually leads to permanent disability.

Primary Progressive Multiple Sclerosis (PPMS) - which makes for 15-20% of cases, is characterized by steady worsening of neurological functioning without distinct relapses.

Progressive Relapsing Multiple Sclerosis (PRMS) - about 10% of cases. It takes the course of relapses along with gradual and significant progression of MS symptoms [11,12].

Clinical symptoms of multiple sclerosis are determined by the location of demyelinating lesions in the nervous system. Initially the symptoms result from the presence of a single lesion. To this group belong: abnormal sensations in the limbs (paresthesia, numbness, pins and needles, hyperaesthesia), optic neuritis (partial or complete loss of visual acuity, scotoma, flashes of light when moving the eyes). Initially, tendon reflexes are preserved, but with the course of the disease they become exaggerated with the presence of Babinski - like responses. Additionally, abdominal reflexes are affected. In the further course of the condition it may lead to pyramidal paresis along with hypertonia, cerebellar symptoms (ataxia, nystagmus, scanned speech, dysdiadochokinesia, intention tremor, dysmetria), brain stem symptoms (dizziness, problems with balance, neuralgia or numbness of face, dysarthria), damage of oculomotor nerves, chronic fatigue syndrome, bladder and bowel difficulties (due to spinal cord damage). In the further course of the disease there is possibility of sexual disorders, cognitive function disorders (problems with concentration and slower information retention) and psychological disorders (emotional lability, depression, pathological laughter and crying). Additional symptoms include feeling pain connected with spasticity of limbs, trigeminal neuralgia, ophthalmalgia, migraine and tension headache [13,14].

Characteristic for MS, seizure-like symptoms are: Lhermitte's sign (an electrical sensation that runs down the back when bending the neck) and Uthoff's phenomenon (temporary problems with sight due to hyperthermia, e.g. hot bath, heat or excessive physical strain) [13,14]

At present, the diagnosis of multiple sclerosis is based on the criteria developed by a panel of experts supervised by McDonald. Among the tests available, most important is the clinical picture of the disease, magnetic resonance imaging (MRI) and the analysis of cerebrospinal fluid [15].

Despite the development of research into better understanding of the essence of multiple sclerosis, the treatment used nowadays is not a selective therapy. Its main function is modifying the natural course of the disease, reducing the number of relapses , alleviating the consequences of relapses and symptoms, and also improving the quality of life of patients.

In the treatment of multiple sclerosis relapses intravenous corticosteroids are used (methylprednisolone in 500-100mg dose, for 3-7 days) , which can be continued with an oral therapy in gradually reduced doses [16].

An important part of therapy is treatment of symptoms which has a great influence on the comfort of patients' life and reduces the number of further complications. It focuses on alleviating various types of symptoms and should always be adjusted to patient's individual needs. Apart from pharmacological treatment (e.g. using baclofen, tizanidine, benzodiazepine in treating spasticity, cholinolytic drugs in case of urinary incontinence caused by the hyperactivity of urinary bladder, simpatico-mimetic drugs in case of distorted functioning of sphincter muscles, amantadine or modafinil in treating chronic

fatigue syndrome, carbamazepine in treating trigeminal neuralgia), important are also non-pharmacological procedures (e.g. rehabilitation procedures, such as hydrotherapy, cryotherapy in treating spasticity, Kegel muscle exercises, using catheters and urinary inserts, treating the patients for dealing with incontinence or retention of urine, educating patients in adapting physical activity in case of suffering from chronic fatigue syndrome) [17-19].

Nowadays the gold standard in treatment procedures of patients with relapsing-remitting multiple sclerosis is immunomodulating treatment. Its aim is to change the natural course of the disease, reduce the number of relapses and in this way slow the progress of neurological disability [20].

Immunomodulating treatment

Idea of immunomodulating treatment is based on the concept of treating multiple sclerosis as an autoimmune disease. Its aim is to modify the natural course of SM, slow its course by reducing the number of relapses. The methods of treatment available nowadays are registered only for the relapsing-remitting multiple sclerosis. To these belong: interferons ß (beta 1a and beta 1b), glatiramer acetate, monoclonal antibody and fingolimod [21].

Interferons

As the first one interferon ß 1b was registered in 1993 in the United States. Interferon ß (IFN-ß) 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 mechanism is about 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 [20,21]. There are slight differences between interferon ß1a and 1b in the way they are built (the length of amino acid sequence) and the way they are produced (IFN-ß 1a is produced by mammalian cells of Chinese Hamster, while IFN-ß 1b is synthesized by modified *Escherichia coli*. Major multicentre randomized clinical research has indicated the effectiveness of interferon ß in remitting-relapsing multiple sclerosis: study by IFNB Multiple Sclerosis Study Group, 1993, PRISMS study (Prevention of Relapses and Disability by Interferon-ß1a Subcutaneously in Multiple Sclerosis, 1998), CHAMPS study (2003), ETOMS study (Early Treatment of SM, 2004), BENEFIT study (2009). They showed the 30% reduction of the frequency of relapses and reduction of active radiological changes in NMR. [22–26]. However, it is still a debatable issue what is the impact of these medications on disability measured by EDSS [27].

At present there are two IFN-ß1a preparations available (30µg intramuscular dosage once a week, or 44µg subcutaneous dosage three times a week) and two IFN-ß1b preparations (250µg subcutaneous dosage every other day).

Glatiramer acetate

It 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. For the treatment of SM it was introduced in 1996 in the United States, and in 2001 in Europe. Similarly to interferons, its exact way of working has not been fully understood. However, it has been discovered that it affects T-cell activation and proliferation (it reduces their reactivity and affects creation of immunoregulative T helper cells (Th2). The copolymer, similarly to interferons, is recommended to patients with relapsing-remitting multiple sclerosis and patients with CIS (Clinically Isolated Syndrome). Clinical studies into effectiveness of glatiramer acetate have also indicated reduced frequency of relapses, but its impact on radiological activity of the disease is less significant [28]. The available glatiramer acetate preparation is in 20µg subcutaneous dosage administered every day.

The course of treatment and care of SM patients on immunomodulating therapy

In Poland a patient with SM can undergo immunomodulating treatment within a programme refunded by the NHS after meeting the inclusion and exclusion criteria [29]. The criteria analyzed include: the length of the disease, the type of he disease, the number of relapses within the last year, neurological state assessed with EDSS. The most important exclusion criteria include: pregnancy, treatment-resistant depression, epilepsy, hepatic failure, thyroid dysfunction (without euthyreosis), hypersensivity to interferon/ glatiramer acetate. An SM patient while qualifying for the treatment is having also various diagnostic tests done: MRI with/ without contrast, biochemical blood tests, general urine test, and in some dubious cases- analysis of cerebrospinal fluid for the presence of immunoglobulin G (IgG). After qualifying for the treatment programme, the patient is provided with medical care by a doctor and a nurse. This allows for monitoring of effectiveness of the treatment. Every three months the patient is undergoing control medical tests (morphology, liver tests), and once a year a MRI test, while during control medical appointments the functional condition of the patient is assessed with EDSS. In case of abnormalities in medical tests, the case managing doctor may decide to reduce the provided dose or to periodically stop the treatment until improvement in the medical parameters is visible. The main tasks of a nurse include preparing the patient for administering the medication

themselves in their homes, dealing with negative side effects of the therapy and supporting the patient and their family during the therapy.

Preparing patients for self-administration of medication in their homes

The nurse that takes care of the SM patient should assess the patient's mobility and neurological deficits. This has an impact on the decision whether to educate only the patient or also their relatives (in case of intensive neurological deficits, a patient will not be able to prepare an administer the medication themselves). The nurse at this point of her cooperation with the patient should also assess his level of knowledge about the disease and immunomodulating treatment, and find out about the patient's socioeconomic status. Collected information will be used in planning an effective educational model which will fully prepare the patient for self-administration of medication [30].

Another step is an instruction about preparing and administering immunomodulating medication.

A very important aspect here is teaching the patients particular stages of the procedure. Special attention must be paid to the way the medication is prepared, they way it is stored (some medication should be stored in the temperature +4°C — +8°C), choosing and marking places on the body where the medication will be administered (stomach, shoulders, thighs, buttock for the medication with subcutaneous injection, front or side part of the thigh for intramuscular injection, avoiding places with skin lesions, painful, irritated or swollen), showing the way of administering the medication (drugs for subcutaneous injection are administered with special autoinjectors, for intramuscular injection with a needle and syringe, important is injecting at a 90 degree angle.) It is also recommended that patients should administer the first injection themselves, as it gives them positive enhancement and helps to overcome their reluctance to self-administering injections. It should be indicated to the patients that all stages of the procedure should be done in accordance with asepsis and antisepsis, and should follow the drilled scheme. The patient should also be taught what to do if it will not be possible to administer the medication right after it was dissolved. In such a case the drug should be put into a refrigerator, bearing in mind that it can only be used for another three hours. After this time it has to be utilized and another dosage should be prepared [31].

The nurse also educates the patient about ways of dealing with possible negative side effects of the treatment. These may include flu-like symptoms (connected with interferon treatment - raised body temperature, headaches, muscle pains, shivering, sweating, feeling 'under the weather") and symptoms connected with the place of injection (red skin, swelling, blushing, local inflammation). When educating the patient it is important to inform them that these symptoms are typically connected with the initial stage of the treatment (last for 4-6 hours after the injection) and subside in the course of treatment. The nurse recommends the patient to take 2 paracetamol pills before making an injection and taking the drug also in the evening which will allow the patient to sleep through the symptoms. To reduce the negative side effects connected with the place of injection it is advisable to recommend the patient to change the place of injection every time and observing their skin after injection. Immediately after an injection is administered a cool gel compress may be applied. To make it easier for the patient to monitor their way of following the procedures, they are asked to run a self-control diary in which they note the date and place of administering the medication and any side affects that appear afterwards. It is important for the patient to understand that following the advice provided by the nurse has an influence on the presence of side effects of the treatment [31].

In case of the patient using glatiramer acetate, it is important to inform them about the possibility of so-called systemic reaction. It is a temporary reaction of the body to a drug which consists in face blushing, heaviness in the chest, palpitation, breathlessness and fear. It is important for the patient to know these symptoms will subside soon, they are present usually after administering the drug (up to 30 minutes) and are not dangerous for them [31,32].

Another aspect of nursing care is supporting the patient and their family during the therapy.

Treatment with immunomodulating drugs should be introduced as early as possible after the diagnosis of the condition. The very information about SM is connected with experiencing negative emotions by the patient, such as fear, anxiety, worry about the future, or anger. Other emotions that the patient experiences are those doubts connected with the suggested therapy: 'Will I manage?' and this is the time when the role of the educating nurse is really significant. On the observation ability, building a relation and trust between the patient and their educator, way of running the educating process depends often the amount of stress and fear that will accompany a patient during the immunomodulating treatment. When a therapeutic bond is built, the patient will not be reluctant to express their problems and worries connected with the therapy [33]. The nurse should focus especially on emotional state

of patients taking interferon medications because of a higher risk of depressive disorders which are side effects of the treatment. In case of the patient experiencing such symptoms (crying, emotional lability, feeling sad), the doctor in charge should be informed and possibly consider changing the treatment (to copolymer or monoclonal antibody) [21]. In the process of educating and supporting the patient, the nurse should also include family and

friends of the patient. Despite the fact that the condition takes individual course, 50 % of patients with relapsing-remitting form of SM after 10-15 years evolve into secondary progressive multiple sclerosis [11]. This is connected with an increased disability and the necessity of greater involvement of family and friends of SM patients. It is often stated that providing care for patients with permanent deficits in their functional states has also negative impact on the caretakers in the form of burden and worsening their quality of life [34,35]. Understanding the essence of the disease, symptoms, possible side effects of the treatment for the caretakers are also important steps in preparing them for the role. The nurse should encourage them to become involved in the education process, observe if they don't experience mood disorders, should check if they are ready for providing caretaker's role, discuss their worries and fears. This enhances the positive bond between the patient and their loved ones [34].

Monoclonal antibody

One of the latest treatments for multiple sclerosis is monoclonal antibody-natalizumab.

It is a humanized monoclonal antibody against the cell adhesion molecule α4-integrin which is found on the surface of lymphocytes and monocytes and takes part in the process of adhesion and transmigration of cells. Natalizumab inhibits lymphocytes crossing blood-brain barrier, and in this way reduces inflammatory process within the CNS. The drug was first registered for treatment of SM in 2004, after a year it was withdrawn from the market and reintroduced in 2006. Nowadays it is used in the therapy of patients with high disease activity, when treatment with interferons and glatiramer acetate proved ineffective [36]. Natalizumab has proven effective in reducing the number of relapses, slowing the progress and radiological activity of the disease [37,38]. The most dangerous complications connected with the use of this treatment include developing progressive multifocal leukoencephalopathy (PML). It is a progressive demyelination of white matter caused by infecting oligodendrocytes with JC virus. It is characterized by the presence of dementia syndrome, problems with mobility, vision, may lead also to coma and possible death. The risk factors of developing PML include: length of treatment < 2 years, using immunosupression before and presence of anti-JC virus antibodies in the patient's serum. While qualifying a patient for the treatment it is important to do medical tests (general urine test, blood smear morphology, biochemical blood tests evaluating working of liver and kidneys, anti-JC virus antibody test and pregnancy test), MRI (with/without contrast) no longer than 30 days before the planned infusion and to assess neurological state of a patient with EDSS [39,40].

Because of high risk of adverse effects, before introducing monoclonal therapy, the doctor together with the patient should analyze advantages and disadvantages of the treatment to be used. The patient should receive a warning card (which they should be carrying with themselves all the time) and information about the product. It is important for the doctor to make sure that the patient understands the possible risk involved and consciously opts for introducing the therapy. As the early symptoms of PML may not be visible for patients themselves (reducing intellectual ability, concentration, behavior changes, and neurological disorders) they may be confused with an SM relapse, so the doctor should also involve patient's family and friends. They should be familiar with the symptoms of PML and observe the patient for the presence of these symptoms.

The patient included in the therapeutic program in accordance with NHS recommendations, should be closely monitored during the whole period of therapy for presence of any adverse effects and lack of effectiveness of the treatment provided. Before each administration of the drug the patient's neurological and psychological state should be checked, medical test should be done (blood smear morphology, parameters evaluating condition of liver and kidneys), general urine tests (every three months in the first year of the treatment, and later, every 6 months), MRI with/without contrast (after each year of therapy), anti- JC virus antibody titer in patients with negative result (every 6 months) [40].

Natalizumab (300mg) is administered for one hour by intravenous infusion once every 4 weeks in 100 ml sodium chloride solution for infusion to 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection. During the infusion and one hour after it, the patient should be monitored for allergic reaction to the medication.

After 2 years of treatment the patients should be once again informed about the risks connected with the treatment, especially about PML risk, the patients and their caretakers should be reminded about early risks of the condition in order to make a joint decision about further treatment[41,42].

In the recent years a new drug has been introduced for treating multiple sclerosis- fingolimod. It is a selective immunosuppressive drug. It is a sphingosine 1-1phosphate receptor modulator, which sequesters lymphocytes in lymph nodes, preventing them from breaking blood- brain barrier to CNS. This is where it connects with nerve cell receptor. Flingolimod sequesters T-cells and B-cells in lymph nodes preventing them from moving to the central nervous system for taking part in inflammatory process [43].

Similarly to natalizumab, the drug is registered in the treatment program of NHS refunded medications for relapsing-remitting form of SM with high activity of the disease, or in cases of patients for whom interferon ß treatment proved ineffective. While qualifying a patient for the treatment into account are taken: patient's neurological state (measured by EDSS), number and severity of relapses and radiological activity of the disease based

on MRI. Exclusion criteria include: patients with higher risk of severe opportunistic infections (e.g. immune deficit syndrome, active treatment with immunosuppressive drugs), patients with diagnosed severe and active infections (e.g. tuberculosis, hepatitis), cancer, ischemic heart disease, sinus node disease, or cardiac infarction. Before introducing the medication, similarly to natalizumab, medical tests have to be done, MRI of head, and, additionally, patients taking ß-blockers, cholinolytic drugs or digoxin should consult a cardiologist. And, similarly, the doctor should discuss with the patient the advantages and disadvantages of the treatment and describe its course [42,43].

The drug is administered in 0,5 mg capsules between meals or during meals. The first dose of the drug is administered in hospital. This is due to the risks of cardiac arrhythmia. After the first dose is administered, it leads to slowing the frequency of heart action, with the lowest frequency within the first 6 hours after administering the drug. For this reason the patient has to be monitored during this time with ECG. Before administering the drug and every hour after finishing the monitoring, life parameters of the patient should be checked (arterial blood pressure and pulse). The parameters should be noted in the patient's medical papers. During regular administration of the drug, heart activity should return to its normal way after about a month [43].

Further doses of the drug the patients administer themselves in their homes. It is recommended to administer the drug at the same time every day so as not to forget about it. It is important for the patient to understand the necessity of taking the drug regularly. The patient must not modify the dosage of the medication. This should also be discussed with the patient.

Preparing the patient for fingolimod therapy it is also important to inform them abort possible adverse effects such as: flu infection, herpesvirus infection, headaches, pain in the back, cough, depressive disorders, arterial hypertension, bowel problems (diarrhoea). The patient should observe their body and if they experience any worrying symptoms, they should consult the doctor or the nurse who are in charge of their therapy [42,43].

Throughout all the therapy the patient should be monitored in a very precise way. Initially at a month, and later at 3, 96, 9, 12 months of treatment, and later not less frequently than every 6 months, a blood smear and liver test should be done. MRI test should be carried out after each year of the treatment. Additionally, after 3-4 months from introducing the therapy an optical consultation should be done (to check for macular edema as a possible complication) and dermatological consultation (after a year of therapy). During control visits, both the doctor and the nurse should talk to the patient and their family about their feelings (somatic and emotional). They should provide support for the patient in difficult moments and set realistic, achievable goals. Such way of working with the patient increases the chances of effective therapy [43].

Conclusion

Multiple sclerosis is a progressive disorder. The treatment should start at the earliest possible moment, right after the diagnosis of SM. For several years on the market different medications have been available: interferons, glatiramer acetate, and the latest ones- natalizumab and fingolimod. Choosing a specific treatment depends on the clinical state of the disease and its progress. The therapy is planned as a systematic and long-term treatment. An important aspect of the therapy is not only preparing the patient for its introduction, but also further observation of its effectiveness and possible adverse effects connected with using the drug. Every stage of the treatment brings new problems and difficulties for the patient. But it is the way that the leading doctor and nurse help the patient through several years of therapy that its effectiveness depends on, and this allows also for maintaining physical mobility and quality of life of the SM patient.

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Corresponding Author:
Anna Smelkowska
Zakład Pielęgniarstwa Neurologicznego i Psychiatrycznego, Uniwersytet Medyczny im. K. Marcinkowskiego,
ul. Smoluchowskiego 11, 60-179 Poznań
e-mail: asmelk@ump.edu.pl

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Author Contributions: Anna Smelkowska[A,B,E,C], Maria Wilkiewicz[A,B,E,C], Barbara Grabowska-Fudala[F,E], Krystyna Jaracz[G,H]
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