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Treatment of multiple sclerosis under the COVID-19 pandemic

KRONIKK

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Patients with multiple sclerosis are often treated with immunosuppressants and frequently have comorbidities or functional decline. They may therefore be at increased risk of a serious course of COVID-19 if they are infected by the SARS-CoV-2 virus. The Norwegian Multiple Sclerosis Competence Centre has drawn up recommendations for treatment of the disease under the pandemic.

The treatment of multiple sclerosis (MS) has changed considerably in recent years. The drugs that are now used can substantially slow the progression of the disease, but the immunodepressant therapy may also affect the course of COVID-19.

The mechanisms of the drugs vary, and so probably does the risk of adverse effects in the event of infection with the SARS-CoV-2 virus. We will summarise here the recommendations of the Norwegian Multiple Sclerosis Competence Centre for treating MS under the pandemic. If there is a choice of treatment, the risk of an MS flare-up must be weighed against the risk of infection and of a severe COVID-19 course. Most patients should continue therapy they have started, in some cases with a longer interval between doses. The

immunosuppressant effect of the drugs is so limited for most patients that the infection prevention measures recommended for the population at large are sufficient.

Disease-modifying therapy

Immunomodulators and immunosuppressant therapy slow the progression of the disease in relapsing-remitting multiple sclerosis (1). Patients with progressive forms of the disease are also treated to an increasing extent, but derive generally less benefit (2). Until recently, the majority of patients started with drugs that have a relatively limited effect and low risk (interferons, glatiramer acetate and teriflunomide), and switched to more effective therapy (fingolimod, natalizumab, cladribine, rituximab, alemtuzumab) if they suffered new relapses or an MRI scan revealed new signs of disease activity. Because prompt commencement of potent therapy has the optimal effect on the long-term prognosis (1), and because the risk associated with several of these drugs appears to be relatively low, potent drugs are now often used as initial treatment.

Glatiramer acetate and interferon-β normally cause little or no immunosuppression. With the partial exception of natalizumab, which specifically inhibits migration of lymphocytes from the blood to the central nervous system, all more potent MS therapies are immunosuppressant (Table 1). However, the degree of immunosuppression varies across drugs and over time, and in most patients is limited or moderate. Autologous haematopoietic stem cell transplantation (HSCT) and alemtuzumab cause immediate, almost full depletion of circulating T and B cells and pronounced immunosuppression, which is strongest in stem cell therapy where other immune cells are also affected.

Table 1

Important properties of different therapeutic options used for multiple sclerosis under the COVID-19 pandemic. The table represents the authors' assessments in mid-April 2020, based on the data presented in the article.

	Efficacy against multiple sclerosis	Immunosuppression due to the therapy	Rebound disease activity on cessation	Start therapy under COVID-19 pandemic	Continue therapy under COVID-19 pandemic	Need for blood tests during treatment
Glatiramer acetate	Limited	No	No	OK	OK	No
Interferons	Limited	No	No	OK	OK	Rare
Teriflunomide	Limited	Limited	No	OK	OK (watch out for granulocytopenia)	Frequent
Dimethyl fumarate	Medium	Limited	No	OK	OK (watch out for lymphopenia)	Rare
Fingolimod	Medium/high	Moderate	Yes	Consider alternative	OK (watch out for lymphopenia)	Rare
Natalizumab	High	Limited	Yes	OK (JCV negative)	OK, intervals can be extended	Rare
Rituximab Ocrelizumab	High	Prolonged moderate	No	Consider alternative	Consider postponing	Rare
Cladribine	High	Prolonged moderate	No	Consider alternative	Consider postponing	Rare
Alemtuzumab	High	High, waning	No	No	Consider postponing	Frequent
Autologous haematopoietic cell transplantation	High	Very strong, declining	No	No	Not relevant	Frequent initially

Immunosuppression declines gradually, so that the immune system of the great majority is fully restored after a few years. Cladribine also inhibits both T and B cells for a long time, but the effect is less pronounced and the immune system will be gradually reconstituted. Antibodies against B cells (rituximab and ocrelizumab) have little effect on T cells and plasma cells and therefore cause less pronounced acute immunosuppression. As the drugs are normally administered at six month intervals, however, the immune system is reconstituted to a lesser degree, and the incidence of severe infections appears to be higher

than with natalizumab (3).

MS therapy and COVID-19

Several groups of experts have pointed out that we do not yet know whether multiple sclerosis therapy influences the risk of being infected or the clinical course of COVID-19 (4–7). However, it is reasonable to suppose that the degree of immunosuppression, manner of administration (infusion in hospital or home therapy), need for monitoring (blood and urine tests, clinical check-ups) and the risk of a sharp increase in disease activity (rebound) if treatment is interrupted may be of importance. Our assessment of these factors for the different MS drugs is presented in Table 1.

As a general rule, we recommend that ongoing treatment be continued for patients with relapsing-remitting multiple sclerosis

It has been concluded in consensual reports that the drugs with the most pronounced immunosuppressant effect are probably the most unfavourable in the event of COVID-19, although there is no scientific evidence for this (4–7). We support this view. Theoretically, antiviral or anti-inflammatory properties of individual MS drugs may be favourable in the event of SARS-CoV-2 infection (7). This is being investigated for interferon-β1a, but at present the findings are too uncertain for weight to be attached to them.

Patients undergoing treatment

As a general rule, we recommend to continue initiated treatment in patients with relapsing-remitting multiple sclerosis. In order to reduce contact with the health service, the intervals between drug dosages administered in hospitals can be increased.

This is particularly relevant for natalizumab, which is administered every four weeks, while the other drugs are administered every six months or less frequently. Observational studies indicate that the therapeutic effect is not reduced when the intervals between natalizumab infusions are increased to up to eight weeks (8, 9). We therefore recommend increasing the interval to six weeks for clinically stable patients who have been treated for at least six months. Breaks in treatment exceeding 8–9 weeks should be avoided, as disease activity then increases and may exceed the level before the start of treatment (10). This happens most frequently in patients with high inflammatory activity prior to starting on natalizumab, and most rapidly in patients with a high body weight (9).

In order to reduce contact with the health service, the intervals between drug dosages administered in hospitals can be increased

For rituximab, the effect appears to persist beyond the usual administration interval of six months (11). We therefore recommend increasing the interval to 9–12 months, depending on previous length of treatment, disease activity and levels of B cells and IgG in younger patients with relapsing-remitting multiple sclerosis, or until the pandemic is over for older patients with progressive disease. Postponement of retreatment with cladribine and alemtuzumab should be considered to prevent unnecessary immunosuppression, but this will depend on the patient's disease activity prior to treatment start, lymphocyte levels, comorbidity and age.

Treatment start

Postponing the start of immunomodulating treatment for multiple sclerosis entails a risk of severe neurological damage (1, 12). Treatment postponement should therefore be avoided, also under the COVID-19 pandemic. The risk is greatest for patients who at the time of diagnosis have many contrast-enhanced MRI lesions and infratentorial and medullary lesions (12, 13).

Natalizumab stands out among the potent drugs in having little general

immunosuppressant effect. Like international expert groups, we also recommend natalizumab at the start of potent MS therapy under the COVID-19 pandemic (4–7). However, the Decision Forum decided in 2019 that natalizumab cannot be offered to new MS patients in Norway. An application for exemption under the pandemic has been sent to regional medical directors.

In carriers of John Cunningham virus (JC virus) natalizumab creates a risk of progressive multifocal leukoencephalopathy. Natalizumab is therefore usually less relevant for these patients, even though an extended dosage interval considerably reduces the risk of progressive multifocal leukoencephalopathy (14). SARS-CoV-2 appears to have neurotropic properties, and one case of meningoencephalitis has been reported. It is not currently known whether natalizumab or other MS drugs increase the risk of COVID-19 encephalitis.

For patients requiring potent treatment who cannot have natalizumab, cladribine and rituximab are the most appropriate, as fingolimod has not been approved by the Decision Forum and alemtuzumab causes prolonged and significant immunosuppression and relatively frequently severe adverse effects (15). Rituximab causes an excess frequency of bacterial infections, while cladribine causes an excess frequency of herpes zoster. We consider both to be justified for patients who have no known tendency to infection or immune deficiency.

Vaccine response

The ability to respond to vaccination may be of major importance if a vaccine against SARS-CoV-2 becomes available. Interferon drugs and glatiramer acetate do not impair the response to the seasonal influenza vaccine (16). Natalizumab has little or no effect on vaccine response (16, 17), while ocrelizumab and probably also rituximab considerably impair vaccine response in MS patients (18). Alemtuzumab and cladribine have a temporary immunosuppressive effect that may reduce the efficacy of vaccine in the period following vaccination, but the majority of patients appear nonetheless to respond to vaccine within a few months following alemtuzumab therapy (19).

MS relapses

Severe MS relapses should preferably be treated in the patient's home with peroral methylprednisolone (Medrol). If, during the preceding fourteen days, the patient has been in places or situations with a high risk of SARS-CoV-2 infection, there should be a high threshold for starting a methylprednisolone course.

Follow-up

To prevent infection transmission, blood tests, MRI scans and contact with doctors should be limited to what may have therapeutic implications. In the current emergency situation, most follow-up can be conducted by telephone. MRI follow-up should be limited to patients with grounds for suspecting a relapse, where this is not evident from clinical findings.

Regular blood tests are recommended for several of the drugs, among other things to monitor lymphocyte and granulocyte levels. In the current emergency situation, the need for these should be assessed on a case-by-case basis. For patients who have been stable for several years, in terms of both clinical presentation and laboratory tests, the benefit may be less than the risk of infection transmission in connection with sample-taking. There is hardly a need to monitor liver tests every 14 days in all patients who start on teriflunomide, as the risk of severe liver damage is very limited.

Postponed start of immunomodulating treatment for multiple sclerosis entails a risk of severe neurological damage

Patients who have been prescribed alemtuzumab must in principle have blood and urine specimens monitored every month for four years to detect secondary autoimmunity

(autoimmune thyroiditis, thrombocytopenia, glomuleronephritis). These adverse effects very seldom appear in the first months after infusion, which is when patients are most immunosuppressed. It may therefore be wise to refrain from routine blood tests for the first 4–5 months after infusion. Patients must then be told to contact a doctor immediately in the event of symptoms such as a tendency to bleed or pronounced malaise.

Hauge et al. recently reported the case of an MS patient on rituximab therapy who developed acute pulmonary failure, and in whom SARS-CoV-2 was detected in bronchial lavage fluid, but not in nasopharyngeal specimens (20). Although the causal relationship between MS therapy and the course of COVID-19 is uncertain, the case report illustrates the importance of diagnostic alertness and that unexpected courses may occur.

Work and isolation

For most MS patients, it will be sufficient to follow the Directorate of Health's guidelines for infection prevention, and the therapy is no obstacle to working or to their children going to school or day care. Special work arrangements or other special infection prevention measures may be relevant for some small patient populations. This applies particularly to patients who have had autologous haematopoietic stem cell transplantation in the last six months or alemtuzumab in the last three months or have persistent lymphocytopenia in addition. The time limits are not absolute, but depend on the patient's age and comorbidity. For stem cell transplantation, the conditioning regimen, which varies across therapy centres, must also be taken into consideration. Special infection prevention measures may also be relevant for patients who use dimethyl fumarate or fingolimod and who have a lymphocyte count lower than the intervention limits ($0.5 \cdot 10^9$/l for dimethyl fumarate and $0.2 \cdot 10^9$/l for fingolimod) and patients who have received cladribine, rituximab or ocrelizumab in the last 6–12 months and who have significant comorbidity (chronic obstructive pulmonary disease, heart disease, cancer, diabetes, hypogammaglobulinaemia or other immune failure), particularly if they are over 50–55 years and have significant functional decline.

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