

Application of Glucocorticoids in Therapy of Multiple Sclerosis

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Abstract. Multiple sclerosis is an autoimmune disease affecting the central nervous system that causes significant disability and healthcare burden. Pulse-dosaged glucocorticoids therapy remains the mainstay of treatment of exacerbations of multiple sclerosis. A total of 98 patients were examined, including 28 patients with relapsing-remitting multiple sclerosis (24 women and 4 men) and 70 patients with secondary progressive multiple sclerosis (57 women and 13 men). The number of glucocorticoids therapy courses in 98 patients at all disease stages totalled 536: 98 in relapsing-remitting multiple sclerosis (9 at debuts and 89 at relapsing-remitting stage) and 438 in secondary progressive multiple sclerosis (11 at debuts, 178 at relapsing-remitting stage, and 249 at secondary progression stage). The efficacy of repeated courses of glucocorticoids therapy in patients with RR and secondary progressive multiple sclerosis

was evaluated at different stages of the disease progression: debut in relapsing-remitting and secondary progressive multiple sclerosis, relapsing-remitting stage in relapsing-remitting and secondary progressive multiple sclerosis, and secondary progression stage in secondary progressive multiple sclerosis, including retrospective analysis. Important conclusions have been made about complex systemic reorganisation at different stages of relapsing-remitting and secondary progressive types of multiple sclerosis, efficiency of glucocorticoids therapy in different types of multiple sclerosis and stages of pathological process and about influence of glucocorticoids therapy on the prognosis of the disease.

Keywords: multiple sclerosis, glucocorticoid therapy, exacerbation, secondary progression, uncertain prognosis.

Introduction. The modern algorithm of multiple sclerosis treatment includes management of exacerbations with glucocorticoids therapy, immunotherapy with multiple sclerosis disease-modifying drugs, symptomatic therapy to eliminate various clinical disease manifestations, and adaptive strategies to develop a set of rehabilitation measures to reduce the degree of disability [1-8].

First-line drugs that manage multiple sclerosis exacerbations are glucocorticoids (prednisolone, methylprednisolone), whose clinical effect is due to their immunosuppressive, anti-inflammatory and anti-oedematous action. Glucocorticoids have a wide spectrum of therapeutic action, influencing immune reactions in various ways: by lymphocytolysis; by accelerating the

catabolism of immunoglobulins; by reducing the production of pro-inflammatory cytokines (interleukins-1, -6, -8 and tumour necrosis factor alpha; by suppressing the transcription and enhancing the degradation of genes controlling the synthesis of interleukin-2, which is central to the development of the immune response; by improving axonal conduction; and by stabilising the permeability of the blood-brain barrier. Recent studies point to the ability of glucocorticoids to inhibit the formation of “black holes” (sites of neuronal death) and prevent the development of brain atrophy. The discovered effects of glucocorticoids prevent early persistent disability by slowing the development of brain atrophy, which is accompanied by a steady accumulation of residual neurological deficit [9-11].

Hormonal therapy in multiple sclerosis is important not only as a factor suppressing the autoimmune process, but also as a type of substitution therapy due to the development of glucocorticoid deficiency, which changes immunological reactivity towards increased allergic manifestations and contributes to the demyelination process. Hyperactivity of the hypothalamic-pituitary-adrenal system in multiple sclerosis is caused by reduced functional activity of glucocorticoid receptors and results in impaired immunoreactivity of the body. At the same time, the experience of using glucocorticoids in multiple sclerosis accumulated over many decades has not solved a series of problems related to their administration. There is no consensus on adequate dosages, regimens, methods and duration of administration taking into account the severity of exacerbations, expediency of prescription in the debut, evaluation of the efficacy of glucocorticoids therapy in isolated use and in combination with other alternative treatment methods. Frequent administration of inadequate hormone regimens by increasing the daily dose of the drug at the next exacerbation contributes to the suppression of the hypothalamic-pituitary-adrenal system, and the development of steroid addiction, which leads to persistent hormone-dependent forms and further progression of the process [1, 3, 12].

A breakthrough in this field occurred in recent decades thanks to the implementation of highly effective pulse therapy with methylprednisolone (Metypred, Solu-Medrol) for the management of relapses in the relapsing-remitting type of multiple sclerosis progression. The drug has a significant advantage over prednisolone due to the presence of a methyl group capable of penetrating the cell membrane and binding to intracellular receptors. Solu-Medrol (Metypred) is administered in high doses (up to 1000 mg) by intravenous drip for 5-7 days. The effect of the drug in the process of restoration of central nervous system functions affected by demyelinating processes is maintained for 1,5 months due to a powerful anti-inflammatory and anti-oedematous action, leading to a significant reduction in brain volume and normalisation of blood-brain barrier permeability [1, 8, 13, 14].

Until recently, the spectrum of therapeutic measures in the secondary progredient type of multiple sclerosis progression was forcefully limited to the use of cytostatics, which cause a significant number of complications in case of long-term treatment [15, 16]. Due to the therapeutic effects of glucocorticoids, the sceptical attitude to their prescription in secondary progredient multiple sclerosis was reconsidered because, unlike relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis is characterised by an unfavourable prognosis because of the progression of the process leading to the accumulation of neurological deficit and persistent disability. It is proved that in this disease type degenerative-axonal lesions are combined with autoimmune inflammatory changes of varying severity. Despite a different temporal algorithm of the inflammatory process development and significant differences between these multiple sclerosis types which are manifested by clinical-immunological and clinical-morphological dissociations (“iceberg phenomenon” according to C. Poser), the activity of the demyelinating process at the secondary progression stage in secondary progressive multiple sclerosis can be comparable with the activity of relapses in relapsing-remitting multiple sclerosis. Therefore, timely and adequate administration of glucocorticoids at early stages of secondary progredient multiple sclerosis, i.e. at the debut and at the beginning of the relapsing-remitting stage, can delay further progression of the process. This statement is the evidence-based justification for the use of active immunosuppressive glucocorticoids therapy in this category of patients at all stages of the disease progression [1, 5, 17].

The purpose of the study was to evaluate the comparative efficacy of hormonal glucocorticoid pulse therapy and to develop an algorithm of differential administration at different stages of relapsing-remitting and secondary-progredient types of multiple sclerosis.

Materials and methods. The study was conducted at the Department of Autoimmune and Degenerative Pathology of the Nervous System at the Multiple Sclerosis Centre of the State Enterprise “Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine”.

The study involved clinical neurological and statistical research methods. The clinical neurological method included retrospective analysis of the disease progression from the manifestation of clinical symptoms in each patient and dynamic neurological examination during periods of relapses and remissions at the relapsing-remitting stage in relapsing-remitting multiple sclerosis and during progression and stabilisation at the secondary progression stage in secondary progressive multiple sclerosis. Statistical processing of the data was carried out using the “Statgraph” statistical software package with a defined number of patients (n), mean index value (M), and the standard deviation of the index (m).

A total of 98 patients were examined, including 28 patients with relapsing-remitting multiple sclerosis (24 women and 4 men) and 70 patients with secondary progredient multiple sclerosis (57 women and 13 men).

The number of glucocorticoids therapy courses in 98 patients at all disease stages totalled 536: 98 in relapsing-remitting multiple sclerosis (9 at debuts and 89 at relapsing-remitting stage) and 438 in secondary progredient multiple sclerosis (11 at debuts, 178 at relapsing-remitting stage, and 249 at secondary progression stage).

The efficacy of repeated courses of glucocorticoids therapy in patients with relapsing-remitting and secondary progredient multiple sclerosis was evaluated at different stages of the disease progression: debut in relapsing-remitting and secondary progredient multiple sclerosis, relapsing-remitting stage in relapsing-remitting and secondary progredient multiple sclerosis, and secondary progression stage in secondary progressive multiple sclerosis, which are of strategic importance for the final prognosis of the disease. The following clinical parameters were considered at different stages of relapsing-remitting and secondary progressive multiple sclerosis: age at onset, disease duration, age and severity of debuts, duration of remission after debut, duration of relapsing-remitting stage, number and severity of relapses at relapsing-remitting stage, mean relapse rate at relapsing-remitting stage, duration of secondary progression stage at the end of the study, progression variants at secondary progression stage, duration of remissions (stabilisation) after the first and before the last glucocorticoids therapy course in relapsing-remitting and secondary progressive multiple sclerosis, progression rate in relapsing-remitting and secondary progressive multiple sclerosis, dynamics of expanded disability status scale disability scale scores after the first and before the last glucocorticoids therapy course in relapsing-remitting and secondary progressive multiple sclerosis [18-20].

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Results and discussion. At the time of evaluation of glucocorticoids therapy efficacy, the age of patients and disease duration in relapsing-remitting multiple sclerosis were significantly lower than in secondary progredient multiple sclerosis ($p < 0.05$), whereas the age of debut in the two disease types was not significantly different (Table 1).

Table 1. Age, disease duration and age at onset in relapsing-remitting and secondary progredient multiple sclerosis (years), $M \pm m$.

| Parameter | Relapsing-remitting (n=28) | Secondary progredient (n=70) |
|-----------|-------------------------------|------------------------------------|
| Mean age | 39.2±2.0 ¹⁾ | 45.9±2.5 ¹⁾ |

| | | |
|-----------------------|-----------------------|------------------------|
| Mean disease duration | 9.5±1.2 ²⁾ | 19.8±2.3 ²⁾ |
| Mean age at onset | 29.5±2.1 | 27.6±2.0 |

Notes: n – number of patients; M – mean value; m – standard deviation; ¹⁾ p<0.05 – significant differences in age between relapsing-remitting and secondary progressive multiple sclerosis; ²⁾ p<0.05 – significant differences in disease duration between relapsing-remitting and secondary progressive multiple sclerosis.

The pattern of debut severity in relapsing-remitting and secondary progressive multiple sclerosis was alternating: mild debuts were predominant in relapsing-remitting and moderate debuts were predominant in secondary progressive multiple sclerosis. Accordingly, a comparative assessment of debut severity between the two types of disease showed a significant predominance of mild debuts in relapsing-remitting and moderate debuts in secondary progressive multiple sclerosis; severe debuts were rare in all patients with almost equal incidence (Table 2).

Table 2. Debuts of varying severity in relapsing-remitting and secondary progressive multiple sclerosis, M±m.

| Parameter | Relapsing-remitting (n=28) | | Secondary progressive (n=70) | |
|-----------------|-------------------------------|------------------------|---------------------------------|------------------------|
| | abs. value | % | abs. value | % |
| Mild debuts | 16 | 57.2±9.3 ¹⁾ | 19 | 27.5±7.4 ¹⁾ |
| Moderate debuts | 10 | 35.7±9.0 ²⁾ | 44 | 62.5±8.1 ²⁾ |
| Severe debuts | 2 | 7.1±4.8 | 7 | 10.0±5.1 |

Notes: n – number of patients; M – mean value; m – standard deviation; ¹⁾ p<0.05 – significant differences in the frequency of mild debuts between relapsing-remitting and secondary progressive multiple sclerosis; ²⁾ p<0.05 – significant differences in the frequency of moderate debuts between relapsing-remitting and secondary progressive multiple sclerosis.

GC pulse therapy at the debut stage was performed in only 21 (21.4%) of 98 patients, including in 9 (32.1±8.8) % of 28 with relapsing-remitting and in 12 (17.1±4.5) % of 70 with secondary progressive multiple sclerosis. Such a low percentage, especially in patients with future secondary progressive multiple sclerosis (2 times less), was due to untimely diagnosis of multiple sclerosis (Table 3).

Table 3. Glucocorticoids pulse therapy at the debut stage in patients with relapsing-remitting and secondary progressive multiple sclerosis, M±m.

| Parameter | Relapsing-remitting (n=28) | | Secondary progressive (n=70) | |
|---|-------------------------------|----------|---------------------------------|----------|
| | abs. value | % | abs. value | % |
| After glucocorticoids therapy administration in relapsing-remitting | 9 | 32.1±8.8 | - | - |
| Without glucocorticoids therapy administration in relapsing-remitting | 19 | 67.9±8.8 | - | - |
| After glucocorticoids therapy administration in secondary progressive | - | - | 12 | 17.1±4.5 |
| Without glucocorticoids therapy administration in secondary progressive | - | - | 58 | 82.9±4.5 |

Notes: n – number of patients; M – mean value; m – standard deviation

The experience of glucocorticoids therapy administration proved its high efficacy in mild and moderate debuts, especially in relapsing-remitting multiple sclerosis. The first course of the glucocorticoids therapy resulted in rapid and significant regression of neurological symptoms and full clinical remission. In the group of patients with severe debuts, which were extremely rare, especially in relapsing-remitting multiple sclerosis, the recovery from debuts was prolonged and accompanied by minimal regression of neurological deficit with the outcome of incomplete clinical remission despite glucocorticoids therapy administration.

Despite the high efficacy of the first glucocorticoids therapy course, no significant differences in the duration of remission after the debut were found in patients with relapsing-remitting and secondary progredient multiple sclerosis, whereas this parameter was significantly higher in patients with secondary progressive multiple sclerosis without glucocorticoids therapy administration (Table 4).

Table 4. Duration of remission after debut depending on the administration of the first glucocorticoids therapy course in relapsing-remitting and secondary progredient multiple sclerosis, M±m.

| Parameter | Relapsing-remitting (n=28) | Secondary progredient (n=70) |
|--|-------------------------------|---------------------------------|
| After glucocorticoids therapy administration | 3.5±1.3% | 5.7±2.8% |
| Without glucocorticoids therapy administration | 2.6±0.8% ¹⁾ | 6.2±2.9% ¹⁾ |

Notes: n – number of patients; M – mean value; m – standard deviation; ¹⁾ p<0.05 – significant differences in the duration of remission after debut in secondary progressive multiple sclerosis without glucocorticoids therapy administration.

The specific features of the relapsing-remitting stage (duration, frequency and severity of relapses, neurological deficit accumulation rate) play a key role in triggering the process of relapsing-remitting stage to secondary progression stage transformation. The implementation of this process requires a complex selective structural reorganisation of clinical indicators at relapsing-remitting stage, among which the severity of relapses is of particular significance. An increase in the frequency of severe relapses during the relapsing-remitting stage is a trigger that accelerates the relapsing-remitting stage to secondary progression stage transformation [19, 21].

According to its duration, relapsing-remitting stage was divided into short (2 to 5 years), moderate (5 to 8 years) and long (more than 8 years). The average duration of relapsing-remitting stage at the background of repeated hormonal therapy courses was (6.8 ± 0.8) years in relapsing-remitting multiple sclerosis and (10.4 ± 3.9) years in secondary progredient multiple sclerosis. Thus, at the time of pulse therapy efficacy evaluation, the duration of relapsing-remitting stage was shorter (p>0.05) in relapsing-remitting multiple sclerosis than in secondary progredient multiple sclerosis due to the incomplete nature of the relapse process and indicated the absence of an immediate threat of its transformation into secondary progression stage.

Neurological symptoms during exacerbation periods at the relapsing-remitting stage affected the leading functional systems with predominance of pyramidal and cerebellar syndromes. As a rule, relapses of different severity (mild, moderate and severe) alternated in the vast majority of patients as the relapsing-remitting stage progressed. Mild relapses were characterised by rapid rates of clinical symptom development, short duration (no more than 3-4 weeks), mono- or oligosyndromic symptoms with minimal signs of rapidly regressing neurological deficit. In moderate relapses, oligo- or polysyndromic symptoms prevailed with the formation of moderate neurological deficit and its subsequent regression at moderate rates (up to 2 or more months). In severe relapses, pronounced polysyndromic symptoms developed, and their partial regression occurred at a slower rate (within 3 or more months), as a rule with the outcome of short and incomplete clinical remissions.

19 of 28 patients with relapsing-remitting multiple sclerosis and 47 of 70 patients with secondary progressive multiple sclerosis were first administered glucocorticoids therapy at the relapsing-remitting stage. As a consequence, all patients with relapsing-remitting multiple sclerosis and 59 of 70 patients with secondary progressive multiple sclerosis received glucocorticoids therapy at the debut or at the relapsing-remitting stage. The other 11 patients with secondary progressive multiple sclerosis first received hormonal therapy at the secondary progression stage due to the absence of the relapsing-remitting stage.

A total of 267 glucocorticoids therapy courses were administered at the relapsing-remitting stage in both patient groups: 89 courses for relapsing-remitting multiple sclerosis (72 for moderate relapses and 17 for severe relapses) in 67.8 % of patients and 178 courses for secondary progressive multiple sclerosis (104 for moderate relapses and 74 for severe relapses) in 84.3 % of patients. The mean number of courses per patient was 3.1 for relapsing-remitting multiple sclerosis and 3.0 for secondary progressive multiple sclerosis.

Thus, hormonal therapy at the relapsing-remitting stage covered the vast majority of patients with moderate to severe relapses. In mild relapses, patients did not receive glucocorticoids therapy despite a significant proportion of this subgroup having radiological activity based on magnetic resonance imaging. Violation of the protocol, according to which hormonal therapy is recommended for all relapses regardless of their severity, led to an increase in the frequency and severity of relapses, accumulation of residual neurological deficits, shortened relapsing-remitting stage duration, and increased risk of relapsing-remitting stage transformation into secondary progression.

The total number of relapses at the relapsing-remitting stage in all patients at the background of repeated courses of glucocorticoids therapy was 505, including 139 (27.5 %) in relapsing-remitting multiple sclerosis and 366 (72.5 %) in secondary progressive multiple sclerosis. The average number of relapses per patient was 4.9 in relapsing-remitting multiple sclerosis and 6.3 in secondary progressive multiple sclerosis. The prevalence of relapses at the relapsing-remitting stage in patients with secondary progressive multiple sclerosis indicates a more unfavourable development of the process and can serve as one of the clinical markers of probable relapsing-remitting stage to secondary progression stage transformation.

The analysis of the frequency of relapses of different severity (mild, moderate, severe) showed no significant differences between relapsing-remitting and secondary progressive multiple sclerosis. During the entire relapsing-remitting stage in the two types of disease progression, the relapses of moderate severity prevailed with the same incidence; mild relapses were more frequent in relapsing-remitting multiple sclerosis ($p > 0.05$); severe relapses prevailed in secondary progressive multiple sclerosis ($p > 0.05$). A significant predominance of moderate over severe and mild over severe relapses was observed in relapsing-remitting multiple sclerosis. In turn, moderate relapses were significantly more frequent than mild or severe relapses in secondary progressive multiple sclerosis (Table 5).

Table 5. Severity of relapses at the relapsing-remitting stage in relapsing-remitting and secondary progressive multiple sclerosis at the background of repeated glucocorticoids therapy courses, $M \pm m$.

| Relapse severity at the relapsing-remitting stage | Relapsing-remitting (n=28) | Secondary progressive (n=59) |
|---|----------------------------|------------------------------|
| Mild | 35.9±9.1% ²⁾ | 28.8±5.9% ³⁾ |
| Moderate | 51.9±9.4% ¹⁾ | 49.1±6.5% ^{3,4)} |
| Severe | 12.2±6.2% ^{1,2)} | 22.1±5.4% ⁴⁾ |

Notes: n – number of patients; M – mean value; m – standard deviation; ¹⁾ $p < 0.05$ – significant differences in the incidence of moderate and severe relapses in relapsing-remitting multiple sclerosis; ²⁾ $p < 0.05$ – significant differences in the incidence of mild and severe relapses in relapsing-remitting multiple sclerosis; ³⁾ $p < 0.05$ – significant differences in the incidence of mild and moderate relapses in secondary progressive multiple sclerosis; ⁴⁾ $p < 0.05$ – significant differences in the incidence of moderate and severe relapses in secondary progressive multiple sclerosis

The mean relapse rate (mean relapse rate – the ratio of the number of relapses to the relapsing-remitting stage duration) was not significantly different between the studied patient groups and was 0.9 ± 0.1 for relapsing-remitting multiple sclerosis and 1.1 ± 0.2 for secondary progressive multiple sclerosis (mean relapse rate for each patient ranged from 0.1 to 2.8). Decreasing mean relapse rate (<1.0) indicated infrequent relapses and longer relapsing-remitting stage duration; increasing mean relapse rate (>1.0) was associated with more frequent relapses and shorter relapsing-remitting stage duration (Table 6).

Table 6. Mean relapse rate at the relapsing-remitting stage in relapsing-remitting and secondary progressive multiple sclerosis at the background of repeated glucocorticoids therapy courses, $M \pm m$.

| Mean relapse rate | Relapsing-remitting (n=28) | Secondary progressive (n=70) |
|-------------------|-------------------------------|---------------------------------|
| <1.0 | $0.6 \pm 0.3\%$ | $0.5 \pm 0.1\%$ ¹⁾ |
| >1.0 | $1.5 \pm 0.9\%$ | $1.6 \pm 0.7\%$ ¹⁾ |

Notes: n – number of patients; M – mean value; m – standard deviation; ¹⁾ $p < 0.05$ – significant difference between mean relapse rate <1.0 and mean relapse rate >1.0 in secondary progressive multiple sclerosis

Relapses were significantly more frequent in secondary progressive multiple sclerosis with mean relapse rate >1.0 than with mean relapse rate <1.0 , whereas there was just a trend between these two parameters in relapsing-remitting multiple sclerosis ($p > 0.005$) (Table 6).

The clinical effect under the influence of glucocorticoids therapy courses was characterised by differentiated regression of neurological deficit. This led to conditional distinction between “well-controlled” and “poorly controlled” symptoms in each functional system. In the pyramidal syndrome, spastic tonus disorders were primarily subject to reverse development, while recovery of leg strength depended on the severity of paresis. In the cerebellar-atactic syndrome, “well-controlled” symptoms included a decrease in the amplitude of horizontal nystagmus and shakiness when walking, as well as an improvement in the performance of the finger-nose test. Performance of the patellofemoral test and static ataxia in the Romberg test were much less frequently subject to reverse development. The regression of sensory disorders was differentiated and depended on their nature. The most “well-controlled” symptoms were disorders of pain sensitivity and astereognosis, whereas normalisation of proprioceptive and temperature sensitivity was slow and, as a rule, partial. In stem disorders, vestibular syndrome, vertical nystagmus, and facial muscle dysfunctions as a result of facial nerve damage were more often subjected to significant regression; less frequently, various oculomotor disorders were observed. Sphincter disorders, depending on the degree of their decompensation, were usually subject to partial regression with significant individual differences.

Thus, the analysis of glucocorticoids pulse therapy efficacy indicates that a “dissociation syndrome” with selective and differentiated regression of clinical symptoms in separate functional systems was developed during relapsing-remitting stage at relapses of varying severity in patients with relapsing-remitting and secondary progressive multiple sclerosis.

The process of relapsing-remitting stage to secondary progression stage transformation occurred as the efficacy of hormonal therapy decreased and proceeded at different rates in different patients. At the time of assessment of glucocorticoids therapy results in 70 patients with secondary progressive multiple sclerosis, the average duration of secondary progression stage was (7.2 ± 1.4) years (ranging from 3 to 17 years).

The number of glucocorticoids therapy courses at secondary progression stage in 70 patients with secondary progressive multiple sclerosis was 249, which on average corresponded to 3.5 courses per patient. There were no significant differences in the average frequency of courses during relapsing-remitting stage and secondary progression stage in secondary progressive multiple sclerosis (3.0 and 3.5, respectively).

Clinical analysis of the secondary progression stage identified the main variants and rates of progression, which indicate its complex structural and functional organisation and are of strategic importance for further disease development and prognosis.

Three main variants of progression have been identified: steady, proceeding without clinically marked stabilisation periods; relapsing, in the form of abrupt exacerbations, resembling relapses, recovery from which was accompanied by stabilisation periods of different duration; and progressive, representing an alternation of the periods of slow progression of neurological symptoms and stabilisation of different duration [7, 20, 21].

The first two variants (steady and relapsing), usually unfavourable, are characterised by the development of gross and persistent polysyndromic neurological symptoms, absence or relative rarity of dissociation syndromes, and a high progression rate. As a result of such development, a deep disability degree and therapeutic resistance to glucocorticoids therapy of varying degrees are developed. The progressive variant of progression is more favourable in comparison with the first two and is characterised by the absence of gross neurological deficit, higher efficacy of pathogenetic therapy, longer period of residual working ability, and better socio-psychological adaptation. The nature of further progression was determined not only by the variants but also by the intensification rates of neurological symptoms – rapid, moderate and slow. In rapid rates, steady and relapsing variants or their alternation prevail; in moderate and especially slow rates, progressive variants prevail.

The analysis of clinical features of the secondary progression stage revealed interdependence between the mean relapse rate at relapsing-remitting stage and variants of secondary progression. The most favourable progressive variant of progression (40.0 ± 5.8 %), which prevailed in patients with mean relapse rate <1.0 , was the most frequent (Table 7).

Table 7. Progression variants in secondary progredient multiple sclerosis.

| Parameter | Secondary progredient multiple sclerosis (n=70) | |
|-----------------------------------|---|------------------------|
| | abs. value | % |
| Progressive variant | 28 | $40.0 \pm 5.8^{1,2)}$ |
| Relapsing variant | 17 | $24.3 \pm 4.5^{1,3)}$ |
| Steady variant | 21 | $30.0 \pm 5.4^4)$ |
| Alternation of different variants | 4 | $5.7 \pm 2.8^{2,3,4)}$ |

Notes: n – number of patients; M – mean value; m – standard deviation; ¹⁾ $p < 0.05$ – significant differences between progressive and relapsing variants of progression; ²⁾ $p < 0.05$ – significant differences between progressive variant and alternation of different variants of progression; ³⁾ $p < 0.05$ – significant differences between relapsing variant and alternation of different variants of progression; ⁴⁾ $p < 0.05$ – significant differences between steady variant and alternation of different variants of progression.

The second most frequent variant of progression was the most unfavourable one, i.e. steady (30.0 ± 5.4 %), which occurred in one half of the patients at mean relapse rate >1.0 , and in the second half at the secondary progression stage development, which followed remission after the debut, bypassing the relapsing-remitting stage. The relapsing variant, which has an intermediate position between the previous variants in terms of its prognostic significance, was observed in (24.3 ± 4.5 %) of patients. In this category of patients, mean relapse rate <1.0 and mean relapse rate >1.0 were almost equally frequent. Very rarely, in (5.7 ± 2.8 %) of cases, alternation of different variants of progression throughout the course of secondary progression stage was observed (Table 7).

When assessing glucocorticoids therapy efficacy in relapsing-remitting and secondary progredient multiple sclerosis at the beginning (after the first course) and at the end (before the last course), the following parameters were taken into account: mean remission duration and (or) stabilisation duration, the dynamics of scores on the expanded disability status scale disability scale, and the rate of progression.

In relapsing-remitting multiple sclerosis, a comparative assessment of average duration of remission was performed after the first and before the last glucocorticoids therapy course at the end of the study when the relapsing-remitting stage was not completed and there was no immediate risk of transformation into secondary progression stage. The studies showed a significant prevalence of average duration of remission after the first course – (2.8 ± 0.8) years (ranging from 6 months to 10 years) versus the last course – (1.5 ± 0.2) years (ranging from 4 months to 3 years).

In secondary progressive multiple sclerosis, the mean remission duration or stabilisation duration during the secondary progression stage was significantly longer (1.8 ± 0.5) years (ranging from 3 months to 5 years) after the first course than before the last course (1.0 ± 0.1) years (ranging from 2 months to 2 years). A comparative analysis of this parameter between the two disease types, a tendency towards predominance after the first course and a significant predominance before the last course was noted in patients with relapsing-remitting multiple sclerosis.

The prevalence of mean remission duration at the initial stages of the disease and its significant decrease at the end of the study despite repeated courses of hormonal therapy indicates the depression of the hypothalamic-pituitary-adrenal system with the development of steroid addiction, which in some patients leads to the depletion of adaptation-compensatory processes and increased risk of transformation into secondary progression stage.

The above finding is supported by the increased degree of neurological deficit according to the expanded disability status scale disability scale in the two disease types. In relapsing-remitting multiple sclerosis, the mean disability score was (2.1 ± 1.1) points (ranging from 1.0 to 3.0 points) after the first course of glucocorticoids therapy and (3.5 ± 0.7) points (ranging from 2.0 to 4.5 points) before the last course. In secondary progressive multiple sclerosis, the expanded disability status scale score was (3.1 ± 0.4) points (ranging from 2.8 to 5.0 points) after the first course and (6.0 ± 0.9) points (ranging from 5.5 to 7.0 points) before the last course at the end of the study. Comparative analysis of the mean expanded disability status scale score after the first and before the last course of glucocorticoids therapy shows a deepening of neurological deficit, especially in patients with secondary progressive multiple sclerosis at the secondary progression stage ($p < 0.05$).

The negative dynamics of expanded disability status scale scores corresponds to such an integral indicator as the rate of progression (the sum of the difference of scores on the expanded disability status scale disability scale between the first and before the last glucocorticoids therapy course for each patient in relation to the total number of patients), which was 1.1 in relapsing-remitting multiple sclerosis and 2.3 in secondary progressive multiple sclerosis.

Based on the findings, criteria for the efficacy of glucocorticoids therapy in relapsing-remitting and secondary progressive multiple sclerosis were developed. High (61.0 ± 9.2) % and moderate (39.0 ± 9.2) % efficacy was obtained for relapsing-remitting multiple sclerosis, and moderate (30.0 ± 5.4) %, low (30.0 ± 5.4) % and no (40.0 ± 5.8) % efficacy was obtained for secondary progressive multiple sclerosis.

With high efficacy of glucocorticoids therapy, the risk of transformation into secondary progression stage was considered minimal, and the mean relapse rate was less than 1.0. The treatment process in these patients was accompanied by a decrease in the duration of debuts and complete clinical remission after the debut. At the background of increasing relapsing-remitting sclerosis duration, mild (more often) and moderate (less often) short or mid-duration relapses, complete remissions between relapses with minimal residual neurological deficit (expanded disability status scale not more than 2.0 points), long-term preservation of full (more often) or partial (less often) working ability prevailed. With moderate efficacy, patients with relapsing-remitting multiple sclerosis were not at immediate risk of transformation to secondary progression stage either (with mean relapse rate values of less than 1.0 (more often) and more than 1.0 (less often)). However, despite repeated courses of glucocorticoids therapy, the course of the relapsing-remitting stage was less favourable in contrast to patients with high treatment efficacy. This was manifested by an increase in the duration of the debut, predominance of incomplete clinical remissions after the debut, an increase in the frequency of relapses of moderate severity during the relapsing-remitting stage, a

gradual increase in neurological deficit (expanded disability status scale from 2.0 to 3.0 points) in remissions between relapses, and partial loss of working ability (Table 8).

Differences in mean remission duration in patients with high and moderate efficacy after the first and before the last glucocorticoids therapy course were not significant. Low rate of progression (1.1) correlated with insignificant negative dynamics of expanded disability status scale disability score between the first and before the last glucocorticoids therapy course (from 2.1 ± 1.1 to 3.5 ± 0.7), which was mainly attributed to patients with moderate efficacy.

In secondary progressive multiple sclerosis, there was no high efficacy at the background of repeated courses of glucocorticoids therapy. Moderate efficacy was obtained in patients with mean relapse rate <1.0 and mean relapse rate >1.0 , whose clinical symptoms at the background of glucocorticoids therapy were characterised by incomplete remissions after the management of debuts of different severity and duration, development of the relapsing-remitting stage of different duration, against which moderate relapses prevailed. After transformation into secondary progression stage, which occurred at a slow pace, progressive (more often) or relapsing (less often) variants of progression were predominant with neurological deficit (< 6.0 points on the expanded disability status scale) and partial or complete loss of working ability (Table 8).

Table 8. Glucocorticoids therapy efficacy in relapsing-remitting and secondary progredient multiple sclerosis.

| Parameter | Relapsing-remitting (n=28) | | Secondary progredient (n=70) | |
|-------------|-------------------------------|----------|---------------------------------|----------|
| | abs. value | % | abs. value | % |
| High | 17 | 61.0±9.2 | - | - |
| Moderate | 11 | 39.0±9.2 | 21 | 30.0±5.4 |
| Low | - | - | 21 | 30.0±5.4 |
| No efficacy | - | - | 28 | 40.0±5.8 |

Notes: n – number of patients; M – mean value; m – standard deviation

Low efficacy was characterised by the development of a short relapsing-remitting stage after the management of severe or moderate long-term debuts, incomplete and short-termed remission. During the relapsing-remitting stage, there was a regular tendency to more frequent and more severe relapses (mean relapse rate > 1.0) with a steady accumulation of neurological deficit. As a result, there was an inevitable transformation into secondary progression stage, occurring in the form of relapsing (more often) or steady (less often) variants of progression with persistent neurological deficit (from 5.5 to 6.5 points on the expanded disability status scale) and complete loss of working ability.

There was no efficacy in some patients with mean relapse rate > 1.0 . In part of these patients, relapsing-remitting stage was absent and secondary progression stage developed immediately after a prolonged and severe debut. This category of patients was characterised by a steady variant of progression that developed rapidly, high scores (more than 6.5 on the expanded disability status scale with profound disability and complete loss of working ability (Table 8). The comparison of treatment results with the nature of prognosis depending on the disease type indicates that patients with an uncertain prognosis are characterised by moderate treatment efficacy, whereas an unfavourable prognosis prevails in patients with low or no efficacy.

The conducted study indicate that hormonal therapy was the most effective in patients with relapsing-remitting multiple sclerosis. Under the influence of repeated courses of glucocorticoids therapy, high and moderate efficacy of treatment was achieved in the form of positive dynamics of most clinical parameters. At different stages of relapsing-remitting multiple sclerosis, there was a rapid and complete regression of the leading syndromes in the debuts, completeness and duration of remission after the debut increased, the number of patients with mean relapse rate <1.0 rose, the duration of the relapsing-remitting stage increased, the frequency and severity of relapses decreased, and minimal neurological deficit was preserved at the background of low progression rate. As a result

of the above reorganisation, the duration of the relapsing-remitting stage was prolonged and the immediate risk of relapsing-remitting stage to secondary progression stage transformation was averted.

In secondary progredient multiple sclerosis, hormonal therapy was less effective and was assessed according to three gradations as moderate, low or no efficacy. With moderate efficacy, the secondary progression stage developed later after the onset of the disease compared to low efficacy. In this process, which was accompanied by a complex structural rearrangement of the leading clinical indicators, the duration of remission after the debut increased, the number of patients with mean relapse rate >1.0 decreased, the duration of the relapsing-remitting stage increased against the background of reduced number of severe relapses, and there was a slow accumulation of neurological deficit. The positive dynamics of these parameters under the influence of glucocorticoids therapy was partial and differentiated, and, despite significant individual differences, led to the development of a progressive variant of progression, which has a more favourable prognostic value.

In patients with low or no efficacy of glucocorticoids therapy, recovery from debuts was prolonged and accompanied by minimal regression of neurological deficit and short remission after the first attack. The duration of the relapsing-remitting stage was shorter and the frequency of severe relapses was higher than in the group of patients with moderate efficacy. This led to an increase in the number of patients with a high mean relapse rate, steady accumulation of neurological deficit, increased rate of progression and rapid development of the secondary progression stage, whose structure is dominated by unfavourable variants of progression (steady and relapsing).

The analysis of the dynamics of clinical symptoms at different stages of relapsing-remitting and secondary progredient multiple sclerosis under the influence of repeated courses of glucocorticoids therapy indicates that the treatment efficacy is closely related to the nature of the disease prognosis. It is known that, in the overwhelming majority of patients, relapsing-remitting multiple sclerosis has a favourable character. However, a variety of variants should be distinguished in relapsing-remitting multiple sclerosis differing in their clinical course and prognostic significance. Thus, the presence of clinical markers indicating the risk of transformation into secondary progredient multiple sclerosis leads to treating the current prognosis in relapsing-remitting multiple sclerosis as uncertain. Progredient types of disease, including secondary progressive multiple sclerosis, are usually characterised by a rapid accumulation of neurological deficit due to the progression of the process with the development of a high degree of disability and an unfavourable prognosis in the vast majority of patients. However, a relatively “benign”, or uncertain, variant of prognosis should also be distinguished in secondary progredient multiple sclerosis, which is characterised by longer relapsing-remitting stage, progressive variant of progression with long periods of stabilisation, slow accumulation of neurological deficit, and positive response to various methods of pathogenetic therapy (glucocorticoids therapy, disease modifying treatment, etc.). Consequently, the prognosis, as an expected result of the previous course of the demyelinating process, depends on the clinical interpretation of the entire disease pattern, including retrospective analysis of disease stages [7, 20, 22, 23].

Clinical and mathematical analysis for the evaluation of the studied indicators in different types of multiple sclerosis resulted in the development of clinical criteria for different prognosis variants: favourable and uncertain for relapsing-remitting multiple sclerosis, and unfavourable and uncertain for secondary progredient multiple sclerosis [23–25].

A comparison of treatment results with the prognosis in relapsing-remitting multiple sclerosis indicates a favourable prognosis with high efficacy and an uncertain prognosis with moderate efficacy of repeated courses of glucocorticoids therapy. In secondary progredient multiple sclerosis, uncertain prognosis prevailed in patients with moderate efficacy, while low or no efficacy under the influence of glucocorticoids therapy suggested an unfavourable prognosis.

Conclusions. Under the influence of repeated courses of glucocorticoids therapy, clinical parameters undergo a complex systemic reorganisation at different stages of relapsing-remitting and secondary-progredient types of multiple sclerosis. As a result of retrospective analysis of the dynamics of clinical parameters occurring in the course of relapsing-remitting and secondary-

progredient multiple sclerosis, criteria for the efficacy of hormonal glucocorticoids therapy were developed: high and moderate efficacy for the relapsing-remitting type; moderate, low and no efficacy for the secondary-progredient type. Treatment efficacy in repeated glucocorticoids therapy courses is closely associated with the nature of prognosis (favourable, unfavourable, uncertain) obtained as a result of clinical and mathematical analysis of indicators characterising different types of multiple sclerosis. In the relapsing-remitting type, high efficacy prevailed for the favourable prognosis, and moderate efficacy prevailed for the uncertain prognosis; in the secondary-progredient type, moderate efficacy correlated with the uncertain prognosis, and low or no efficacy correlated with the unfavourable prognosis. High efficacy of glucocorticoids therapy in patients with relapsing-remitting multiple sclerosis with a favourable prognosis was characterised by complete clinical remissions after the debut, predominance of mild short relapses at the relapsing stage, minimal neurological deficit, low progression rate, long-term preservation of working ability, and minimal risk of transformation into the secondary-progredient type. With moderate efficacy of glucocorticoids therapy in patients with an uncertain prognosis, the probability of transformation into the secondary-progredient type increased due to decreased compensatory reserves of the body. In this process, the duration of debut and the prevalence of incomplete clinical remissions after debut increased. At the relapsing-remitting stage, relapses of moderate severity prevailed against the background of a gradual increase in neurological deficit with partial loss of working ability. In the secondary-progredient type, the efficacy of treatment with repeated courses of glucocorticoids therapy was significantly lower than in the relapsing-remitting type, but the process of transformation of the relapsing-remitting stage into secondary progression occurred at different rates and was characterised by significant individual differences. In the case of an uncertain prognosis, moderate efficacy prevailed, which led to a decrease in the number of severe relapses against the background of increased duration of the relapsing-remitting stage and the development of a more favourable progressive variant of progression. The unfavourable prognosis was characterised by low or no efficacy. These subgroups of patients showed no positive dynamics of most clinical parameters at all stages of the disease. As a result, a steady or recurrent variant of progression, a pronounced neurological deficit, and a high degree of disability were developed. The expediency of timely administration of and treatment with repeated courses of glucocorticoids pulse therapy in patients with relapsing-remitting multiple sclerosis with a favourable and uncertain prognosis and in patients with the secondary-progredient type with an uncertain prognosis has been proved. In case of low efficacy in patients with secondary progredient multiple sclerosis type and an unfavourable prognosis, it is necessary to develop new approaches to the multiple sclerosis treatment strategy.

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References.

1. Gusev E.I., Boiko A.N. Multiple sclerosis: from studying immunopathogenesis to new treatment techniques. M.: Gubernskaya Medicine, 2001. 128 p.
2. Gusev E.I., Zavalishin I.A., Noiko A.N. Multiple sclerosis and other demyelinating diseases. M.: Miklosh, 2004. 540 p.
3. Levin O.S. Immunotherapy of multiple sclerosis. *Russian Medical Journal*. 2001. No.6. P.48-52.

4. Yevtushenko S.K., Derevyanko I.N. Current approaches to the treatment of multiple sclerosis: achievements, disappointments, hopes (2nd communication). *International Neurological Journal*. 2006. No.2 (6). P.2–12.
5. Compston A. The pathogenesis and basis for treatment in multiple sclerosis. *Clin. Neurol. Neurosurg.* 2004. Vol.106. No.3. P.246-248. URL: <https://pubmed.ncbi.nlm.nih.gov/15177777/>
6. Dobson R., Giovannoni G. Multiple sclerosis – a review. *European Journal of Neurology*. 2018. Vol.26. No.1. P.27–40. URL: <https://doi.org/10.1111/ene.13819>
7. Voloshyna N.P., [Taitslin V.I.] A. H. Leshchenko A.H. et al. Multiple sclerosis in Ukraine: prevalence, course, prognosis, treatment, pharmacoconomics. *Ukrainian Bulletin of Psychoneurology*. 2007. Vol.15, Iss. 1(50). P. 6–21.
8. Voloshyn P.V., Voloshyna N.P., [Taitslin V.I.] et al. Current aspects of multiple sclerosis: pathogenesis, peculiarities of disease course in Ukraine, diagnosis, standards of pathogenetic therapy. *Neuron-Review (Journal of Clinical Neurosciences)*. 2007. No. 3. P. 4-26.
9. Tarianyk K.A., Shkodina A.D., Lytvynenko N.V. et al. Combined therapy of relapsing-remitting multiple sclerosis exacerbations with plasmapheresis and glucocorticoids with regard to patients' quality of life. *Ukrainian Neurological Journal*. 2020. No. 3. P. 29–34. doi 0.30978/UNJ2020-3-29. URL: <http://ukrneuroj.com.ua/article/view/UNJ2020-3-29>
10. Voloshyna N.P., Nehreba T.V., Vasylovskyy V.V. et al. Comparative efficacy of hormonal pulse therapy in relapsing-remitting and secondary-progressive types of multiple sclerosis with different prognosis patterns. Communication I. Efficacy of hormonal pulse therapy in the debut and relapsing phase in relapsing and secondary-progressive types of multiple sclerosis with different prognosis patterns. *International Neurological Journal*. 2018. No. 4(98). P. 21–31. URL: <http://www.mif-ua.com/archive/article/46247>
11. Voloshyna N.P., Nehreba T.V., Vasylovskyy V.V. Comparative efficacy of hormonal pulse therapy in relapsing-remitting and secondary-progressive types of multiple sclerosis with different prognosis patterns. Communication II. Efficacy of hormonal pulse therapy in the progression phase in the secondary-progressive type of multiple sclerosis with different prognosis patterns. *International Neurological Journal*. 2018. No. 7(101). P. 14–16.
12. Douglas S., Hudin H. Glucocorticoids for the treatment of multiple sclerosis. *Handb Clin Neurol*. 2014. No.122. P. 455–464. doi: 10.1016/B978-0-444-52001-2.00020-0. URL: <https://pubmed.ncbi.nlm.nih.gov/24507531/>
13. Sharrack B., Hughes R., R. Morris R. et al. The effect of oral and intravenous methylprednisolone treatment on subsequent relapse rate in multiple sclerosis. *J. Neurol. Sci.* 2000. Vol.1. No.173(1). P.73–77. URL: <https://pubmed.ncbi.nlm.nih.gov/10675582/>
14. Alam S.M., Kyriakides T.M., Lawdwn P.K. Newman methylprednisolone in multiple sclerosis. *J. Neurol.* 2008. No.56. P. 1219–1220.
15. Voloshyna N. P., Vasylovskyy V.V., Chernenko M.Ye. Use of mitoxantrone in combination with cortixin for the treatment of progressive multiple sclerosis. *International Neurological Journal*. 2008. No. 6(22). P. 13–16. URL: <http://www.mif-ua.com/archive/article/7508>
16. Vasylovskyy V.V., Voloshyna N.P., Nehreba T.V. et al. Efficacy of mitoxantrone in patients with progredient types of multiple sclerosis. *International Neurological Journal*. 2015. No. 7(77). P. 17–27.
17. Poser Ch. Multiple sclerosis. *S.S. Korsakov Journal of Neurology and Psychiatry*. 1993. No. 4. P. 77–78.
18. Zavalishin I.A., Zakharova M.N., Peresadova A.V. et al. Progressive course of multiple sclerosis. *S.S. Korsakov Journal of Neuropathology and Psychiatry*. 2002. No. 2, special issue. P. 26–31.
19. Nehreba T.V. Comparative clinical characteristics of debuts and relapse stages in relapsing-remitting and secondary-progressive multiple sclerosis. *Ukrainian Bulletin of Psychoneurology*. 2004. Vol. 12. Iss. 1 (38). P. 66–69.
20. Nehreba T.V. Course and prognosis of modern forms of multiple sclerosis. *Ukrainian Bulletin of Psychoneurology*. 2006. Vol. 14. Iss. 1(46). P. 44–46.

21. Copyright for a scientific work No.47786 dated 13.02.2013. Voloshyna N.P., Vasylovskyy V.V., Levchenko I.L. et al. New approaches to the clinical diagnosis of different types of multiple sclerosis and their differentiated therapy. Practical recommendations.
22. Copyright for a scientific work No.39160 dated 14.07.2011. Nehreba T.V. Prognostic criteria for different types of multiple sclerosis.
23. Voloshyna N.P., Nehreba T.V., Vasylovskyy V.V. et al. Development of prognosis depending on the development of the progression stage and progression options in progressive types of multiple sclerosis. *Ukrainian Bulletin of Psychoneurology*. 2021. Vol. 29. Iss.3(108). P. 18–22.
24. Voloshyna N.P., Nehreba T.V., Vasylovskyy V.V. et al. Clinical and mathematical analysis of relationships between prognosis and debut patterns in different types of multiple sclerosis. *Georgian medical news*. 2021. No.9(318). P. 127–133.
25. Voloshyna N.P., Vasylovskyy V.V., Kirzhner V.M. et al. Correlation analysis between clinical parameters in different types of multiple sclerosis. *Ukrainian Bulletin of Psychoneurology*. 2022. Vol.30. Iss.1(110). P. 21–27. doi: <https://doi.org/10.36927/2079-0325-V30-is3-2022-94>