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Rationale and experience with combination therapies in multiple sclerosis

Abstract Standard immunomodulatory therapies for multiple sclerosis reduce relapses by around thirty percent and possibly slow progression of disability. In many patients, use of such treatments allows the disease process to be stabilised and quality of life to be improved. However in patients experiencing frequent severe relapses, for whom prognosis is often poor, they may not be sufficiently efficacious. Emerging therapies such as natalizumab, alemtuzumab or mitoxantrone may be more effective in such patients but have potentially greater side-effects that limit their use as maintenance therapies. Combining current immunomodulatory treatments with emerging therapies may offer the potential to treat patients with active disease successfully and safely. In particular, the use of induction therapy with mitoxantrone followed by maintenance treatment with glatiramer acetate appears to be of interest. In a cohort of over 60 patients receiving this combination in routine clinical practice, disease activity as measured by relapses is rapidly suppressed and the benefit sustained for over five years. With current, anti-inflammatory, therapies decisions on switching and combining therapies need to be made early in the disease course in order to optimise benefit for patients and minimise the risk of accumulating irreversible disability.

Key words multiple sclerosis · combination therapy · beta-interferon · glatiramer acetate · mitoxantrone

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Introduction

Both inflammatory and neurodegenerative processes are implicated in the disease course of multiple sclerosis and the two processes are closely imbricated. In its early stages, disease evolution appears largely related to inflammatory demyelination manifest clinically as relapses. These relapses, however, contribute to axonal injury, demyelination and persistent disability. When a certain level of persistent disability has been reached, perhaps corresponding to EDSS 4 [5], axonal degeneration and disability progression appear to proceed independently of relapses and suppression of inflammation [4]. Nonetheless, in recent years, use of sophisticated magnetic resonance imaging (MRI) techniques have allowed markers of axonal degeneration to be identified early in the disease process before the irreversible progression of disability becomes clinically manifest [7].

This has important implications for treatment. Interventions need to be made early in the disease process to prevent relapse-related disability with the ultimate aim of limiting irreversible axonal degeneration in the belief, or perhaps hope, that this will delay or prevent conversion to the progressive phase of the disease. Currently, all available therapies are broadly 'anti-inflammatory'. Strategies directed at neuroprotection and repair remain elusive and are not likely to be available for some years. Therefore, current drugs need to be used early, when inflammatory processes dominate the disease within the relapsing-remitting phase. In patients with particularly aggressive disease, or who fail to respond to monotherapy, combinations of anti-inflammatory treatments should be considered early, a strategy which echoes the current approach to other auto-immune inflammatory disorders such as rheumatoid arthritis.

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Current therapies

Current licensed therapies for multiple sclerosis consist of the β-interferons and glatiramer acetate. The β-interferons have now been in routine use for over ten years. β-Interferons have a modest effect in relapsing-remitting multiple disease, with a mean reduction in relapse rate of around 30 %. Data on the effects of β-interferons on disability progression are limited, and the effects of these agents in secondary progressive disease are equivocal. A significant minority of treated patients are apparent non-responders. This heterogeneity in response to β-interferons is due in part to the appearance of neutralising antibodies [13] and may also involve inter-individual differences, which are being explored using a pharmacogenomic approach [19]. There are multiple potential mechanisms of action for β-interferons [12], which may involve inhibition of cytokine production from immune cells in the periphery, prevention of immune cell infiltration into the central nervous system and possibly inhibition of cytokine production within the nervous system.

Glatiramer acetate has been available in Europe for up to seven years, depending on when it was approved. The effects of glatiramer acetate on relapses are of a similar magnitude to those of β-interferons. A prospective long-term follow-up study over ten years of pivotal trial patients [10] suggests that this benefit is sustained and possibly improves over time, although interpretation of such open-label uncontrolled data is limited by inevitable drop-outs. Again the mechanism of action of glatiramer acetate appears complex, involving both peripheral effects related to changes in phenotypic expression of T_H cell populations and central effects related to bystander suppression of inflammation and release of neurotrophic factors [8, 12].

Emerging therapies

A number of other therapies have shown effectiveness in multiple sclerosis but are either not approved in this indication or not widely used as routine treatment for early-stage disease. Of particular interest are those therapies that appear to provide a more robust reduction in relapse rate than do the β-interferons and glatiramer acetate.

Mitoxantrone is a cytostatic drug originally developed for the treatment of myeloid leukaemia. It suppresses proliferation of T cells, B cells, and macrophages, as well as inhibiting proinflammatory cytokines and antibody production [11]. Compared with β-interferons, and depending on the dosing regimen, mitoxantrone provides a 70 % to 90 % reduction in relapse rate over the short to medium term. The generalised use of mitoxantrone as a standard maintenance treatment for multiple sclerosis is, however, not possible due to the risk of dose-related cardiotoxicity and of therapy-emergent leukaemia. For these reasons, the use of mitoxantrone to date has been largely restricted to patients who fail conventional therapy.

Alemtuzumab (*Campath-1H*) is a humanised monoclonal antibody directed at the CD52 surface antigen on certain white blood cell populations, which triggers destruction of cells bearing the target antigen resulting in profound and sustained lymphopenia [26]. Again, this treatment was originally developed as an anticancer therapy, in this case for the treatment of chronic lymphocytic leukaemia. Open-label studies in multiple sclerosis have shown a reduction in relapse rate of around 90 % in patients with very active relapsing multiple sclerosis and compete suppression of inflammatory disease activity as measured by MRI [3, 4]. In 23 patients receiving two (nineteen patients) or three (four patients) annual treatments with alemtuzumab, the mean annual relapse rate declined from 2.21 before treatment to 0.19 afterwards, with only ten post treatment investigator-confirmed relapses occurring [4].

In an as yet unpublished comparative study, treatment with alemtuzumab provided a 75 % reduction in relapse rate compared with patients receiving β-interferon 1a *sc* (http://www.msaa.com/articles/article36.htm). As with mitoxantrone, treatment with alemtuzumab is associated with significant potential side-effects. Treatment can provoke iatrogenic autoimmune disease, specifically auto-immune thyroid disease and idiopathic thrombocytopenic purpura, the latter resulting in one death in the head-to-head study. The risks of long-term treatment beyond two to three years are unknown.

An important message from clinical experience with alemtuzumab is that outcome appears to depend on when treatment is initiated during the disease process. In relapsing-remitting disease, disability as measured by EDSS tends to improve or remain stable following treatment with alemtuzumab, whereas disability continues to progress in patients whose disease has already converted to a secondary progressive course [4].

Natalizumab (*Tysabri*) is a monoclonal antibody directed at adhesion molecules on the vascular epithelium that blocks entry of immune cells into the central nervous system. A large placebo-controlled trial [21] demonstrated a reduction in relapse rate of 68 %, associated with reductions in MRI markers of disease activity and risk of disease progression. However, in clinical trials of natalizumab in multiple sclerosis and Crohn's disease, three cases of progressive multifocal leucoencephalopathy were reported, of which two were fatal [1]. It is suggested that this complication of this novel therapy may be due to impaired immune surveillance resulting from closure of the blood-brain barrier to immune competent cells [25]. Again, the risk of long-term use of this agent beyond two years is uncertain.

Combination therapies

Rationale for combination therapies

Currently, the physician has the choice between, on the one hand, four immunomodulatory treatments belonging to two classes which, whilst moderately effective, are not so in all patients and may not be sufficiently efficacious to control very aggressive disease and, on the other, more powerful treatments which have not been validated for use as maintenance therapy and raise serious tolerability issues. Moreover, once patients have been established on immunomodulatory maintenance therapy with β-interferons or glatiramer acetate, adherence to treatment remains an issue. In randomised clinical trials, discontinuation rates vary between 15 % and 25 % over a two to three year period. In everyday practice, discontinuation rates may be higher. We undertook a review of 194 patients with relapsing-remitting multiple sclerosis initiating treatment with one of the four licensed therapies in our clinic between 1996 and 2002 [17]. The mean treatment duration was 5.5 years. At the latest follow-up point available, over half of the patients treated with β-interferons had either discontinued therapy, switched or moved on to combination treatments (Fig. 1). For glatiramer acetate, adherence seems to be better, with two-thirds of patients still treated with this agent at the end of the observation period.

Finally, in patients with very active disease, even if the relapse rate is reduced with first-line monotherapy with immunomodulatory agents, relapses will still occur and disability accumulate, such that the patient is not managed satisfactorily and stopping criteria for treatment failure will be met.

Given that the physiopathology of multiple sclerosis is complex, involving different disease processes evolving in parallel, it would be rational to combine treatments with potentially complementary mechanisms of action targeting different aspects of the disease process. In particular, combining a 'priming' treatment with one of the emerging treatments, which cannot be used as long-term maintenance therapy for safety reasons, followed by maintenance therapy with a β-interferon or glatiramer acetate is particularly attractive.

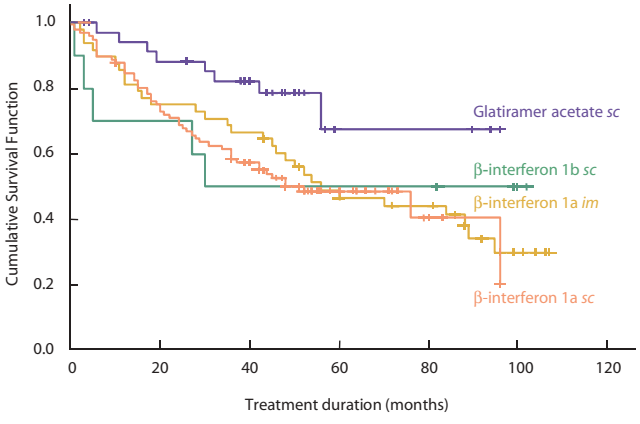

Fig. 1 Treatment discontinuation rates in clinical practice with three β-interferons and glatiramer acetate. Data are presented as Kaplan-Meier survival curves. The cross-strokes indicate censored data

A parallel can be made with recent advances in rheumatoid arthritis, another autoimmune disease which was considered as untreatable one or two decades ago. Treatment practice now consists of identifying patients at risk for rapid progression and stratifying treatment accordingly. Active disease is targeted early using an intensive anti-inflammatory treatment approach to obtain tight control over disease activity. This associates the use of biological agents such as the anti-TNFα (etanercept, infliximab) with a standard immunosuppressant such as methotrexate. Once disease remission is obtained, treatment can be downgraded to maintenance therapy. Such an 'induction-maintenance' strategy is challenging previous 'step-up' strategies, where patients were started on a first-line monotherapy and then switched to a more aggressive therapy or to a combination in case of inadequate control of disease activity. Using such an intensive approach early, it is possible to achieve complete clinical and radiological remission of initially active rheumatoid arthritis within two years in around fifty percent of patients. If such a success rate could be achieved in active multiple sclerosis, this would be a major breakthrough in patient care and it is thus worth considering a similar strategy.

When considering combination therapies for multiple sclerosis, several points should be taken into consideration. Firstly, combining treatments with potentially complementary mechanisms of action should be envisaged. Secondly, the choice of drugs should take into account disease factors, with respect to disease duration, disease activity, clinical phenotype (relapsing-remitting or progressive disease) and previous treatment experience. Thirdly, the safety of the combination needs to be optimised, although it may not always be possible to predict all potential risk and indeed some level of risk may be acceptable in patients with particularly active disease and poor prognosis. Finally, in order to use resources as effectively possible, it is preferable to test combinations first of all in well designed pilot studies which can generate information on different outcome parameters and safety before moving on to large-scale randomised clinical trials that require more resources but provide detailed information on a more restricted set of outcome measures.

Nonetheless, there are several issues that need to be addressed when considering performing a combination study. The first relates to identifying the target patient population in the absence of reliable prognostic markers of disease progression. Due to the necessarily impre-

cise risk-benefit ratio, these treatments need to be offered in priority to patients who are at high risk of early disability. It is equally desirable to initiate treatment early and make use of the window of opportunity that exists in early relapsing-remitting multiple sclerosis to influence disease before substantial irreversible neurological deficits are acquired. However, the shorter the disease duration, the less information we have on natural history and the less confidence we can have in determining prognosis. The choice of which patients to treat will thus be a necessary trade-off between the desire to treat early and the need to ensure that the patient indeed has active disease. Secondly, we have an incomplete understanding of the mechanism of action of the available drugs, making it difficult to predict with certainty the impact of novel drug combinations on immune function and what potential safety issues might arise. There are also a number of design issues, related to powering of studies, to choice of outcome measures, to choice of an appropriate comparator group and to the need for randomisation. Observational studies and randomised controlled trials will both have a role to play in determining the interest of a given combination.

Combination of β-interferon and natalizumab

The only large-scale randomised study of a combination therapy in multiple sclerosis that has been completed and published is the SENTINEL study of natalizumab and β-interferon 1a *im* [24]. This study randomised 1200 patients experiencing continuing disease activity on β-interferon to treatment with either β-interferon 1a *im* alone or β-interferon 1a *im* combined with natalizumab (300 mg *iv* monthly) for two years. The study demonstrated a 55 % reduction in relapse rate in the combination group compared to β-interferon 1a *im* treatment alone, as well as improvements of a comparable magnitude in disease progression measured with the Multiple Sclerosis Functional Composite scale and on MRI markers of disease progression. The study clearly showed that outcome in patients receiving natalizumab was better than in those receiving β-interferon 1a *im* alone. This finding is not inherently surprising, given the results of the placebo-controlled trials of the two agents used in monotherapy. However, the study design did not allow conclusions to be drawn concerning the added benefit of the combination compared with natalizumab alone. This is a critical point, since the two cases of fatal viral encephalopathy in multiple sclerosis patients treated with natalizumab were both observed in patients receiving the combination with β-interferon 1a *im*.

Other combinations with β-interferons

There are a number of other combination studies that have been performed or are currently underway with β-interferons. Several pilot studies have evaluated the combination of β-interferons with the immunosuppressant drug azathioprine [9, 20, 23]. These studies have generally shown the combination to be safe and to provide potential additional benefit in terms of both clinical and MRI outcome measures compared to β-interferon therapy alone. Larger studies to confirm these findings are currently underway.

Adding mitoxantrone in patients responding sub-optimally to β-interferons has also been attempted. A small pilot-study using MRI outcome measures [18] has suggested that addition of mitoxantrone to these patients does indeed improve outcome, although a subsequent study [6] found that this benefit was not maintained and that reactivation of the disease occurred within 12 to 18 months after discontinuing mitoxantrone in the majority of patients. Experience in our centre has also indicated that disease activity usually flares up again quickly once patients return to β-interferon monotherapy. A randomised controlled induction study is currently recruiting in Europe in which patients are randomised either to β-interferon 1b or to a short-term induction with mitoxantrone for three months before switching to β-interferon 1b for maintenance therapy.

An open-label study has been performed to evaluate combination therapy with weekly oral methotrexate and β-interferon 1a *im* in patients who continued to experience relapses with β-interferon 1a *im* monotherapy [2]. The results were consistent with a reduction in disease activity measured on MRI and in relapse rates following addition of methotrexate. A randomised trial to replicate these findings in a larger group of 900 patients is currently underway in the USA.

A large study has been set up by the National Institute of Health in the USA to compare outcome in patients treated with a β-interferon, glatiramer acetate or a combination of the two. This study, which included 1,200 patients, was principally designed to perform a head-to-head comparison of the two treatments but will also provide important information on whether outcome will be superior in patients receiving the combination than in those receiving monotherapy.

Combination of glatiramer acetate with mitoxantrone

In Liverpool, we have treated a series of patients with very active relapsing-remitting disease with induction therapy with mitoxantrone followed by maintenance therapy with glatiramer acetate. The success of this treatment strategy in a group of patients with very ac-

tive multiple sclerosis has led us to propose it systematically to patients whose disease presents with frequent and severe relapses.

The treatment protocol we now use consists of monthly mitoxantrone treatments at a dose of 20 mg for three months followed by two further quarterly doses of 10 mg mitoxantrone, representing a total dose of 80 mg (48 mg/m^2) over an eight month period. From the fifth month, treatment with glatiramer acetate is initiated, overlapping with mitoxantrone for the final two doses, and continued thereafter as maintenance therapy.

This treatment protocol has evolved with experience and has been used successfully in over sixty patients. Data for 27 of these patients are presented in Fig. 2. Two-thirds of these patients were treatment-naïve, whereas six had failed initial treatment, due to continuing relapse activity, with a β-interferon and the remaining two had failed glatiramer acetate. The longest disease duration before treatment was three years, during which time the patients experienced around two steroid-treated relapses a year. After initiation of treatment, relapse rate was reduced by 90 %, with only seven relapses being observed in the entire cohort, mostly in the first few months of treatment. Importantly, the reduction in relapse rate persisted throughout the maintenance phase for an observation period up to 6.5 years. The only two relapses occurring during the maintenance phase were observed in the two patients who had previously failed to respond satisfactorily to monotherapy with glatiramer acetate. In addition, at the most recent follow-up, disability scores in all patients had remained stable or improved since mitoxantrone treatment was initiated. Although it was not possible to collect MRI data systematically during this case series, MRI scans were obtained for the first ten patients around 2.5 years after the beginning of the maintenance phase. Reassuringly, no enhancing lesions were observed on any of the scans and the overall T2 lesion load was substantially reduced compared to pre-treatment. No adverse events were observed relating to the combination treatment phase, which was generally well-tolerated.

These findings, though uncontrolled, suggest a synergistic effect between mitoxantrone and glatiramer acetate. It would be expected that mitoxantrone should suppress disease activity for between 12 to 18 months after the end of treatment, whereas the reduction in relapse rate by glatiramer acetate is around 30 %. The observation of a sustained 90 % reduction in relapse rate for periods over five years suggests that the combination of the two treatments provides a greater benefit than the sum of the individual components. The clinical benefit provided by this induction protocol differs considerably from previous experience with combinations of mitoxantrone with β-interferons, where disease activity returned following discontinuation of mitoxantrone.

The notion that mitoxantrone and glatiramer acetate may have synergistic actions in multiple sclerosis is perhaps supported by preclinical research using the ABH mouse chronic relapsing allergic encephalitis model [22]. This model has interesting face validity for human multiple sclerosis, presenting a relapsing-remitting early phase, acquired disability after several relapses, followed by a progressive disease course. Following disease induction, treatment after the first or second clinical relapse to induce T cell depletion with either CD52 antibodies or mitoxantrone followed one week later by intravenous administration of the disease triggering antigen, spinal cord homogenate, completely suppresses further disease activity. If glatiramer acetate acts in the human disease as a myelin-related antigen, then prior

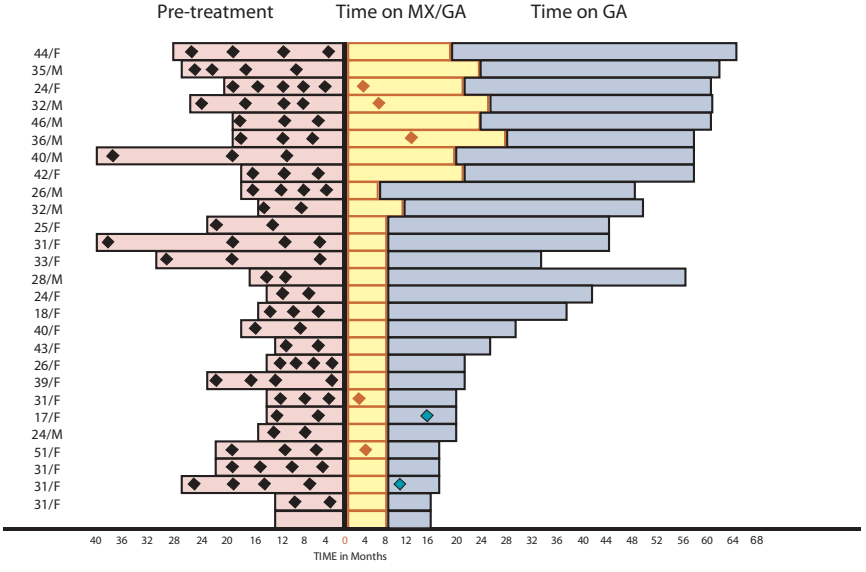

Fig. 2 Treatment outcome in patients with early-onset aggressive multiple sclerosis. Each line represents an individual patient. The x-axis represents the duration of follow-up, normalised to the moment when mitoxantrone treatment was initiated. The pink sections indicate the pre-treatment period, the yellow sections the mitoxantrone induction treatment period and the blue sections the glatiramer acetate maintenance treatment period. The lozenges indicate the timing of individual relapses

immunosuppression may potentially have a similar effect in abrogating multiple sclerosis.

However promising the results of this treatment approach may appear, they raise several issues. Firstly, there is the risk associated with mitoxantrone exposure. The risk of cardiotoxicity, though thought to be dose related, has been estimated at 1 % and that of therapy-related leukaemia at 0.25 % [14]. The risk of infertility in women treated with mitoxantrone, though likely to be small in younger patients at the doses used in our patients, is difficult to estimate. In women over 35 the risk of secondary amenorrhea may be as high as 10 %. In a cohort of over 160 patients treated with this agent in our centre, the drug has been surprisingly straightforward to use, no cases of cardiotoxicity have been identified though a single non-fatal case of acute pro-myelocytic leukaemia occurred in a patient who received 110 mg mitoxantrone. Nonetheless, in order to limit risk, we have found that the duration of mitoxantrone treatment can be substantially reduced without compromising the clinical benefit.

The data obtained from our case series is clearly observational and thus open to unquantifiable selection bias. For this reason, the findings merit replication in a randomised clinical trial, where such biases can be controlled. Finally, outcome in this cohort and subsequent patients needs to be carefully followed over time in order to assess whether the clinical benefit associated with early and robust suppression of inflammatory activity is sustained over the longer term.

In order to gain further insight into the potential of the combination of mitoxantrone and glatiramer acetate induction regimens in multiple sclerosis, two further trials have been initiated. The first, the NC100 study, compares a short induction regimen followed by glatiramer acetate to glatiramer acetate alone in 40 patients with relapsing-remitting disease. Three doses of mitoxantrone are given with no overlap between the induction and maintenance phases. The primary objective of the study is to generate safety and MRI data.

The second study is the United Kingdom Early Mitoxantrone Copaxone Trial, currently being undertaken in ten centres in Great Britain. This study plans to randomise between 60–100 patients to treatment with either combination treatment or β-interferon 1a *sc* 44 µg for a period of three years. The treatment regimen is illustrated in Fig. 3. The entry criteria were designed to select patients who are at high-risk for rapid progression by inclusion of simple clinical markers that are known to be associated with poor prognosis in the medium-term (Table 1). The primary outcome measures are sustained EDSS progression and the Multiple Sclerosis Impact Scale (MSIS-29), a patient-reported outcome measure with excellent psychometric properties shown to be substantially more sensitive to disease changes than EDSS [15, 16].

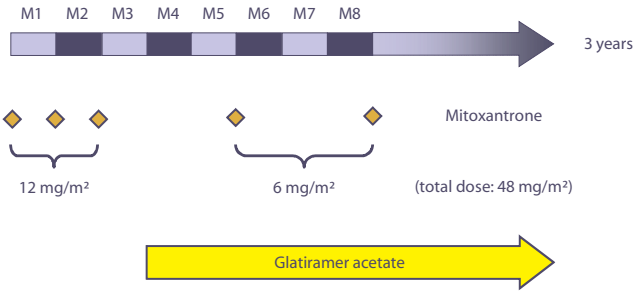

Fig. 3 Dosage regimen in the UK study

Conclusions

Current and emerging therapies for multiple sclerosis offer a range of possibilities to explore therapy combinations in relapsing-remitting disease. The major 'window of opportunity' for all current therapies is in early inflammatory disease and the use of combinations later in the disease once conversion to a progressive course has occurred is unlikely to be effective and may indeed expose patients to inappropriate risk. Before initiating combination therapy, the risks of therapy need to be carefully weighed against those of the disease for each individual. Decisions on treatment, treatment failure, switching or combining therapies need to be made early in order to ensure that patients obtain maximum benefit from current treatments.

Table 1 Inclusion criteria in the UK study

Patients must present	… and 3 of the following
• Disease duration < 5 years	• 3 or more relapses in first 2 years from onset
• EDSS 0–5.5	• Residual disability from early attacks (EDSS > 1.5)
• 2 relapses in last 2 years	• Motor features (pyramidal/ataxia) in early attacks
• …	• 10 or more lesions on brain MRI

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