

Multiple Sclerosis

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Revolution and evolution in multiple sclerosis treatment and care

Professor Tomas Olsson, MD

Enthusied by the possibility of really treating the condition, multidisciplinary teams are making a difference in the lives of MS sufferers. Research and development are the basis for the good news.

This supplement focuses on current and future disease modifying drugs in Multiple Sclerosis (MS). Developments in the field have been remarkable over the last 15 years or so, both with regard to availability of disease-modifying drugs, and the interest shown by neurologists as well as the pharmaceutical industry. This is illustrated by the number of people attending “The European committee for the treatment of MS - ECTRIMS” which attracted around 50 researchers 20 years ago. Now each annual meeting draws more than 3,000 participants.

The appearance of drugs that modify the course of MS has changed several things.

First, MS used to be regarded as an orphan disease with very limited potential for the pharmaceutical industry to profit from sales of new drugs. Now it is apparent that realistic pricing is acceptable and companies can make a profit. A large array of companies has promising drugs all the way from the preclinical setting up to active testing in phase II and III trials. It is even sometimes problematic to find enough patients for recruitment to the clinical trials.

Second, in most countries, the availability of drugs that modify the course of MS has led to more active care for people with the condition. Instead of a neurologist saying “come back when you are worse”, the new treatments require a stringent diagnosis and a structured follow-up of patients. This has led to formation of MS teams. These often contain a neurologist, a MS nurse, a physiotherapist, a social worker, an occupational therapist, psychologist and urology therapist. These different disciplines reflect the fact

that MS affects a person’s whole life with effects on family and relationships, ability to work, etc. Frequent, improved, patient assessment has led to better symptomatic treatment of general signs and symptoms of MS such as depression, fatigue, pain, spasticity and urinary bladder problems.

Until very recently, drugs such as interferon-beta preparations and glatiramer acetate had a proven, but modest, effect against MS relapses demonstrated over two to four years. Since people with MS mostly have the disease for several decades, and in view of the high costs and side effects, it is highly desirable to get long-term data. This cannot be collected in placebo-controlled trials. The challenge is to develop better post marketing surveillance systems, perhaps in web-based systems, to evaluate long-term beneficial and side effects.

As discussed in this supplement the newcomer making the difference is natalizumab (Tysabri). This monoclonal antibody interferes with the immune system with high selectivity for a specific adhesion molecule, VLA4. The efficacy of this drug is very encouraging, demonstrating that it is indeed possible to treat MS more effectively, setting a gold standard against which to test new therapies. However, natalizumab can only be considered to be semi-selective since it does not target disease mechanisms unique to MS. Extravasation of leucocytes is needed also in the defence against infections. Still, perhaps surprisingly, there was little difference in the frequency of common infections between placebo and active drug-treated individuals during the two year trial. Instead, progressive multifocal leucoencephalopathy (PML) ensued in three individuals who were either being

treated concurrently with interferon-beta or were otherwise immuno-suppressed. So use of natalizumab will be restricted to more serious cases of MS, at least initially. The profession should develop strict post-marketing surveillance systems to catch rare adverse events such as PML, or other surprises that may appear with the new drugs, such as fingolimod (discussed by Dr Fontoura on pages 4-5). These data should also be used in a way that the adverse events can be contrasted with natural co-morbidities due to the disease, and not the drug. Such comparisons can be done in countries with well developed population registries.

If this is done there is no risk that a drug with beneficial effects against a particular disease may be abandoned due to a primarily disease-related co-morbidity.

The intense development in the field is likely to result in a much broader spectrum of disease-modifying drugs within a few years. Most of them will probably interfere with various constituents of the immune system. This will increase the need for a sound understanding of immunology by prescribers and pharmacists. It will also give the clinicians a wider, but perhaps more difficult, choice of drugs to offer each individual patient.

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Current treatment with interferon-beta and glatiramer acetate for multiple sclerosis

Professor Sten Fredrikson, MD, PhD

Over the last decade there has been an important conceptual switch in the management of multiple sclerosis (MS) and we have entered a new therapeutic era. Clinical trials have established interferon-beta and glatiramer acetate as first-line disease-modifying drugs in relapsing-remitting MS.

Introduction

Before starting to discuss the effects of the established disease-modifying therapies for multiple sclerosis (MS), i.e. interferon-beta (IFN β) and glatiramer acetate (GA), it is important to remember that most of the treatment trials in patients with MS have not resulted in new therapies in this disease. Some drugs with a theoretically attractive rationale, e.g. anti-TNF α -blockers, showed paradoxical effects with increased disease activity, while others had to be abandoned due to lack of treatment effects or unacceptable side effects. These failed experimental therapies emphasise the positive benefit/risk results achieved in trials with IFN β and GA.

There is a need to develop treatments directed specifically against axonal damage.

Another important prerequisite for the development in the field of MS therapy is the improved and more generally accessible magnetic resonance imaging (MRI) technique. This allows objective comparisons at group level of brain lesions in patients treated with a drug or placebo. The improved MRI technique has also changed the diagnostic criteria for MS, enabling an early diagnosis within weeks or months after the first documented symptoms [1].

Interferon-beta (IFN β) for relapsing remitting MS

IFN β is a naturally occurring cytokine with immunomodulatory and antiviral properties. There are several class I clinical trials showing a beneficial effect on relapse

Table 1: Routes of administration, dosages and manufacturers of available interferon-beta (IFN β) drugs and glatiramer acetate (GA)

| | Route of administration | Dosage | Manufacturer |
|--|-------------------------|----------------------------------|--------------|
| Interferon-beta (IFNβ) | | | |
| Betaferon (IFN β -1b) | SC | 250 μ g every other day | Schering AG |
| Avonex (IFN β -1a) | IM | 30 μ g once weekly | BiogenIdec |
| Rebif (IFN β -1a) | SC | 22/44 μ g three times a week | Serono |
| Glatiramer acetate (GA) | | | |
| Copaxone | SC | 20 mg every day | Teva |

frequency in relapsing-remitting MS (for review see reference [2]). The drugs are generally considered to reduce the relapse frequency by approximately 30%. The IFN β drugs have also been

shown to have a substantial effect in reducing the numbers of new lesions and delaying the increase of total lesion load seen on brain MRI scans. The effect on long term disability and in secondary progressive MS, unless there are concomitant relapses, is less well studied and more uncertain. In some small studies of primary progressive MS, IFN β drugs have not been shown to be clinically useful. Table 1 summarises available IFN β drugs.

The most frequent side effects of IFN β are “flu-like symptoms” with muscle pain and fever or local injection-site reactions. If side effects occur at initiation of treatment, they usually subside or disappear after some weeks.

A question that has been discussed a lot over the years is the optimal dosage and frequency of administration of IFN β . Some studies (EVIDENCE, INCOMIN) have suggested a better effect with higher dose and higher frequency of administration [3, 4]. Another controversial question is the impact of neutralising antibodies (NAbs) that can be found in some patients after IFN β injections. Some studies have shown that NAbs in high titres can influence the clinical effect of the drugs, while other studies have shown that the NAbs may fluctuate and disappear over the years if they have occurred at low levels.

Glatiramer acetate (GA)

Glatiramer acetate is a polypeptide of 4 amino acids based on the composition of myelin basic protein. Several putative immunological mechanisms have been discussed including generation of GA-reactive T helper 2 (anti-inflammatory) cells and a possible neuroprotective effect.

GA has, in a class I study, been shown to reduce the relapse rate in relapsing-

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remitting MS by approximately 30% [2]. Other studies have shown beneficial effects on MRI parameters. The most frequent side effects of GA are usually mild and include local injection site reactions with pain, but also more generalised or systemic reactions, including sweating, palpitations and shortness of breath.

Early treatment of Clinically Isolated Syndrome (CIS)

It is known from previous studies of the natural history of MS, that a high frequency of clinical relapses over the first years is associated with an increased risk of later deterioration. Based on this observation and the inflammatory reactions described in MS there are reasons to initiate treatment as early as possible to prevent axonal damage and irreversible damage. There have been three large clinical trials performed to evaluate the effect of IFN β treatment after the first clinical isolated syndrome (CIS). Avonex

mechanisms of such drugs could be neuroprotective and restorative. None of the available drugs has been approved for treatment of primary progressive MS. An important question that awaits a solution is whether MS is one or several diseases, with different underlying pathogenetic mechanisms.

An interesting, but still debated and unresolved question, is whether some of the inflammatory response in MS brains also has a beneficial and potentially neuroprotective effect. If this is the case, it seems reasonable to find therapies which are not "too immunosuppressive", but have a moderate immunomodulatory function that allows also the neuroprotective immunity to exist.

Disease-modifying treatment of MS with IFN β and GA is a long-term treatment modality that will continue for years. This means that the motivation and compliance is critical for patient

Conclusion

The introduction of interferon-beta and glatiramer acetate has changed our view of multiple sclerosis from being a disease where the biological course could not be influenced into a treatable disease. These first available drugs have opened up a door and initiated a race to find new and potentially even more efficient drugs.

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An important question that awaits a solution is whether MS is one or several diseases, with different underlying pathogenetic mechanisms.

and Betaferon have been registered for initiation of treatment after the first clinical event suggestive of MS [5, 6]. A trial of GA in CIS patients is underway.

Future challenges and the need for new therapies with different mechanisms of action and delivery

The available IFN β and GA drugs are considered to be mainly immunomodulatory and directed towards the immunological processes involved in MS. Recent findings have highlighted that there is also a degenerative component of the disease with axonal damage, probably secondary to the early inflammation. Even if early initiation of immunomodulatory treatment is a logical step to prevent the subsequent neurodegeneration, there is a need to develop treatments directed specifically against the axonal damage. The putative

adherence. Since the drugs are mainly acting prophylactically (and are not supposed to take away already existing disability), patients may need support to be encouraged to remain on therapy. Although it may be risky to evaluate the effects of drugs in MS in daily clinical practice, since the relapse frequency varies between patients, there seems to exist "responders" and "non-responders" to the disease-modifying drugs. An important future improvement of drug usage would be a reliable biomarker, e.g. a blood test, that could reveal if the patient responded to the drug or not. At present, no laboratory marker, including MRI scans, can be used to fully evaluate the treatment effect in an individual patient. It would definitely be a step towards a "tailor made" treatment if such a bio-marker became available.

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New and emerging options on the therapeutic horizon for multiple sclerosis

Paulo Fontoura, MD

Thanks to a new understanding of the pathophysiology of multiple sclerosis new agents such as monoclonal antibodies and oral immunomodulatory agents are now in clinical development.

Introduction

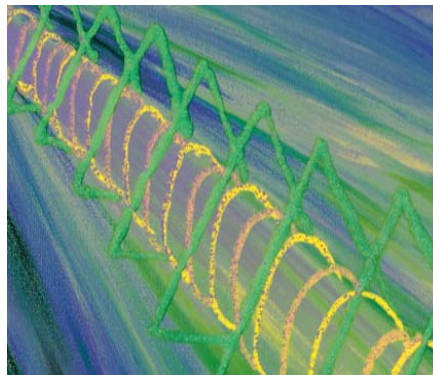
Multiple sclerosis can be conceptually divided into two distinct, but overlapping, pathological stages. The widely accepted standard model of multiple sclerosis (MS) pathophysiology proposes that in the initial inflammatory stage, an autoimmune response against Central Nervous System (CNS) myelin predominates, leading to focal destruction of myelin and axons. This is followed by a progressive, degenerative, stage, characterised by widespread axonal loss and atrophy. This model is based largely on experimental data coming from the animal model of rodent Experimental Autoimmune Encephalomyelitis (EAE), which focuses on the inflammatory stage of the disease; there is a relative paucity of clinical data coming from MS patients [1].

MS therapies are almost exclusively aimed at controlling inflammation, exemplified by the currently approved immunomodulatory (interferon, copolymer-1) and immunosuppressive drugs (mitoxantrone, cyclophosphamide). Development of new therapies has progressed slowly, and several promising drugs with good experimental results in animal models have failed at later stages of clinical development [2]. Despite these setbacks, the EAE model has continued to serve as a source for pathophysiological insight and new therapeutic targets (Figure 1) [3].

Monoclonal antibodies in MS

The recently approved anti-adhesion molecule monoclonal antibody natalizumab (Tysabri) (reviewed in this series) is the first example of a new drug that has progressed from the EAE model and a successful clinical development programme to patient use [4]. Setting aside natalizumab, we will briefly review some other drugs in

advanced stages (II/III) of clinical development that may also make a difference in the near future.



Other monoclonal antibodies being studied as MS therapies include alemtuzumab (Campath-1), rituximab (Rituxan) and daclizumab (Zenapax) [5]. Alemtuzumab causes lysis of CD52+ cells (T and B lym-

phocytes, monocytes and macrophages) reduction but not on progression. However, in one of these trials, a very high incidence (27%) of autoimmune hyperthyroidism was reported, including nine cases that required thyroid radioactive ablation therapy [6]. Since this adverse effect has not been reported when alemtuzumab is used in cancer therapy, this side effect is probably specific for MS therapy, and related to the underlying immune system dysfunction. A randomised, open label, phase II trial of alemtuzumab in comparison with interferon beta is currently in progress in early relapsing-remitting MS patients (CAMMS223 trial). Preliminary results from this trial have revealed similar dramatic effects on relapse rate, but three cases of idiopathic thrombocytopenic purpura (1 fatal) were also reported [7]. In summary, alemtuzumab is definitely effective at suppressing inflammation in MS, but there are

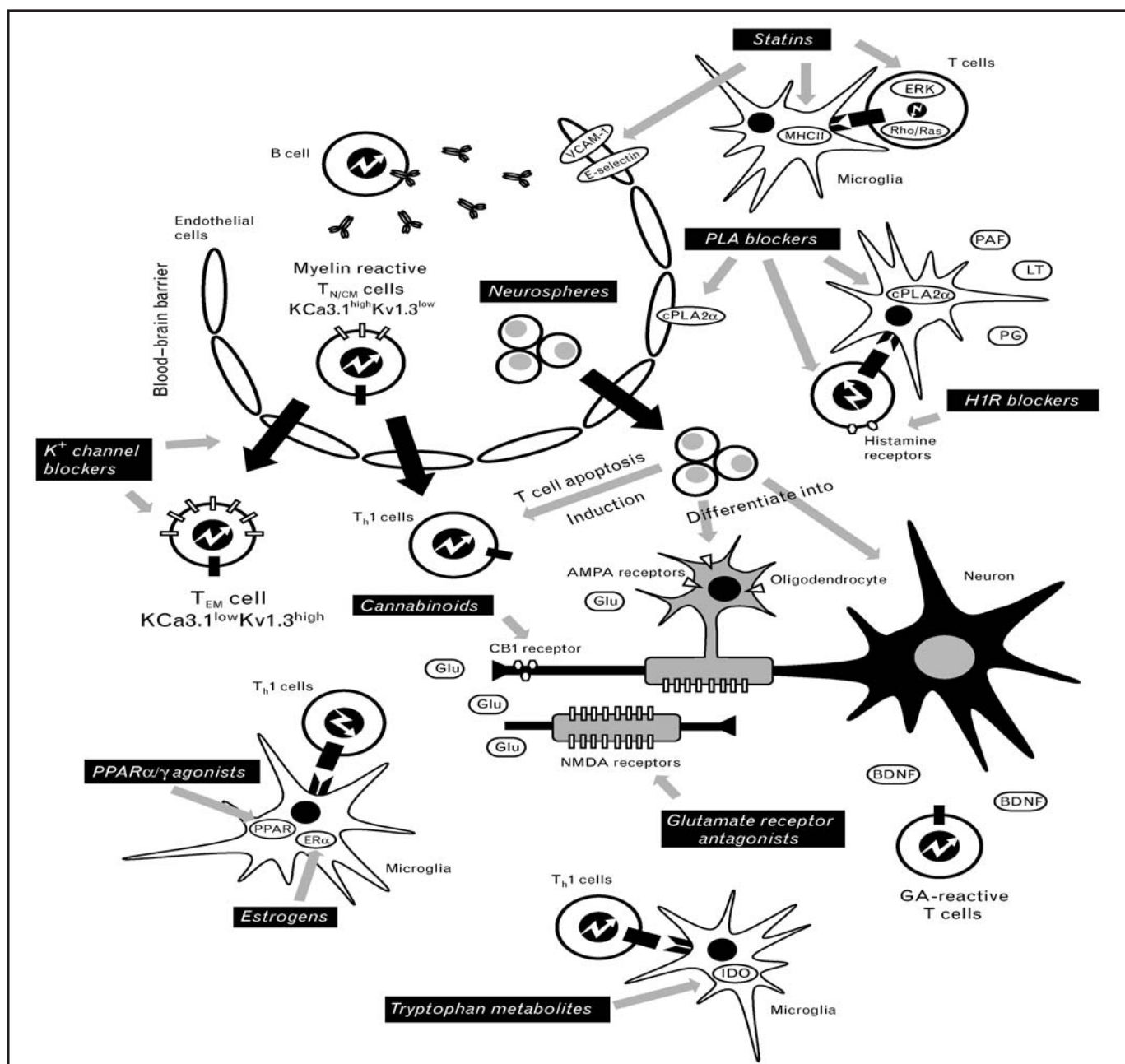
In the initial inflammatory stage of MS, an autoimmune response against Central Nervous System (CNS) myelin predominates. This is followed by a progressive, degenerative stage.

phocytes, monocytes and macrophages) and is an extremely potent immunosuppressant, as reflected by the high incidence of severe infusion reactions and increased risk of infection. Currently, it is approved for the treatment of chronic lymphocytic leukaemia resistant to fludarabine. Development of alemtuzumab for MS treatment is based on the concept of immune reconstitution, whereby elimination of the autoimmune lymphocytic repertoire is followed by the re-establishment of immune tolerance. In the few open-label trials conducted so far, alemtuzumab has showed powerful effects in relapse rate

still uncertainties about the side effect profile and potential for the induction of other autoimmune disease.

Rituximab targets CD20, a cell-surface antigen specific for B and pre-B cells, leading to the depletion of this population. Currently, it is an approved therapy for non-Hodgkin's lymphoma, with a well-known safety and side effect profile. Given the prominent role of the humoral immune response in some forms of MS, rituximab is being actively studied as an MS treatment, with phase II trials in relapsing-remitting and primary progressive MS currently

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⇒ **Figure 1: The rodent Experimental Autoimmune Encephalomyelitis (EAE) model is the current basis of our understanding of multiple sclerosis and its possible treatment**

under way. Interestingly, in an aggressive subtype of MS, neuromyelitis optica, normally unresponsive to therapy, in which the humoral response is thought to predominate, a small open-label study showed promising results [8]. Finally, daclizumab is directed against the cell-surface receptor for interleukin IL-2, and suppresses lymphocytic proliferation by acting as an antagonist for this receptor. This drug is normally used in combination with standard immunosuppressants in kidney trans-

plant rejection. A few, small, open label trials in MS as add-on therapy to interferon-beta have been conducted, with some positive results, but more data is required before any conclusions can be drawn [5].

Oral immunomodulatory agents in MS

The development of orally active MS drugs is the main focus of several efforts to develop alternatives to currently available therapies. Among the agents in advanced stages

of development are cladribine, fingolimod (FTY720), oral fumarates (BG-12) and teriflunomide. Cladribine is a purine analogue that causes lymphocytic death after intracellular phosphorylation to a triphosphate deoxynucleotide by deoxycytidine kinase. Clinical trials of cladribine in MS date back to the early 1990s, both in relapsing-remitting as well as progressive forms of the disease (reviewed in [9]). Cladribine was found not to affect progression on a phase III multicentre, randomised, double-

blind, placebo controlled trial, even though it reduced the burden of disease revealed by MRI (magnetic resonance imaging) [10]. In relapsing-remitting MS, small-scale phase II trials showed promising results in relapse rate reduction, and a multicentre phase III trial of oral cladribine is in progress (CLARITY trial). As with other classic cytotoxic immunosuppressants, there is increased risk of myelosuppression and infections in cladribine-treated patients.

ment of two multicentre phase III, randomised, placebo-controlled, double-blind trials of BG-12 in relapsing-remitting MS, both alone (DEFINE trial) and in comparison to copolymer-1 (CONFIRM trial) [13]. Lastly, teriflunomide, a metabolite of leflunomide, is an inhibitor of pyrimidine synthesis in T cells and other rapidly dividing cell populations. This immunomodulator has shown efficacy in several animal models of autoimmune disease, and data from a

Alemtuzumab is effective at suppressing inflammation in MS, but there are still uncertainties about the side effect profile and potential for the induction of other autoimmune disease.

Fingolimod (FTY720) is an oral sphingosine-1-phosphate receptor modulator that induces lymphocyte sequestration at secondary lymphoid organs, thereby stopping immune cell migration to the CNS. Results from a randomised, placebo-controlled phase II trial of two doses of fingolimod in 255 relapsing-remitting MS patients were recently reported [11]. In this trial, administration of fingolimod for six months resulted in significant suppression of disease activity as measured by MRI, as well as a reduction in the year-adjusted relapse rate. The drug was generally safe, with upper respiratory tract infection, headache, diarrhoea and nausea being the most common side effects, and one case of posterior reversible encephalopathy syndrome in the high-dose cohort. Based on these results, a large-scale phase III multicentre trial is currently taking place in several countries, comparing the efficacy of fingolimod against intramuscular interferon-beta in relapsing-remitting MS (TRANSFORMS trial). Of all the oral agents in development, this is probably the one that has excited the most interest in recent years, not only due to its novel mechanism of action, but also because of its favourable efficacy/side effect profile.

phase II trial in relapsing-remitting and secondary progressive relapsing MS, has recently been published [14]. In this 36-week trial involving 179 patients, testing a low and high dose of teriflunomide, there was a significant reduction in MRI measurements of disease activity, as well as a trend towards reduction in relapse rate and disability in active treatment groups; no important adverse events were reported. A phase III trial is in the initial recruitment stages [15].

Conclusions

There is a clear need to improve the existing MS treatment portfolio. In recent years, several new immune-based therapies have progressed from experimental models to clinical development. Among the most promising are monoclonal antibodies with very potent and selective mechanisms of action, as well as orally active agents with more widespread biological effects, but better tolerability, safety, and convenience of use. It is hoped that the several phase III trials in progress lead to the approval of new effective drugs for treating this challenging neurological condition.

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Clinical aspects of protein drugs

Joep Killestein, MD, PhD; Professor Chris Polman, MD, PhD

In this article the limitations, safety and tolerability concerns of biopharmaceuticals, focusing particularly on natalizumab and interferon-beta, are discussed. The propensity of these drugs to induce neutralising antibodies and the clinical consequences this might have are also addressed.

Introduction

The number of newly approved biopharmaceuticals and promising protein drugs under investigation is rapidly increasing. However, the clinical application of these agents can be associated with particular safety concerns, sometimes occurring early in drug development, as in the case of the experimental drug TGN1412 [1], but also arising at a much later phase, as observed in clinical trials testing natalizumab (a monoclonal antibody against interferon-alpha 4 integrins) alone and especially in combination with other immunomodulatory drugs like interferon-beta [2].

Safety, tolerability and immunogenicity of monoclonal antibodies

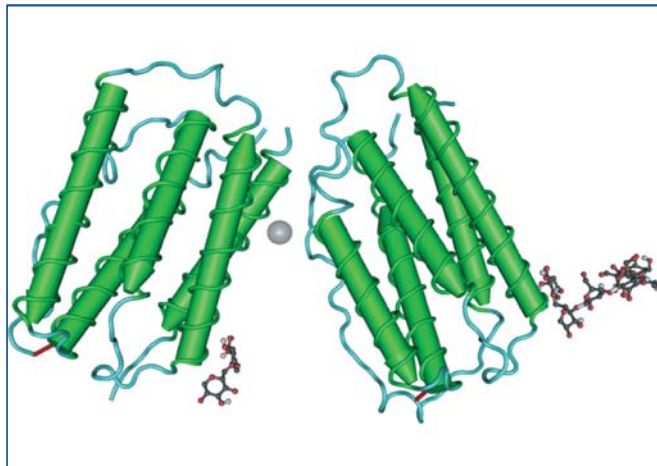
Expertise with monoclonal antibodies (MAbs) has progressed remarkably in the past decades, starting with mouse MAbs, followed by mouse-human chimeric and, most recently, completely human MAbs. The attraction of such drugs derives from the fact that any toxicity is likely to be related to their specific mechanism of action, whereas conventional small-molecule compounds may have chemical toxicities in addition to mechanism-related adverse effects [3]. Despite their molecular precision, monoclonal anti-antibody treatment can have unforeseen effects and even fully human engineered proteins can be immunogenic. The antibodies can neutralise the desired therapeutic effect and in addition, may induce allergic

reactions. After binding to their target, MAbs may induce a systemic inflammatory response. For example, the monoclonal antibody Campath-1H, which is directed against the CD52 antigen on leukocytes, typically induces an influenza-like syndrome, attributed to the systemic release of inflammatory mediators. In addition, even though their molecular targets are precisely known, MAbs may give rise to serious infections and/or development of neoplasms, probably due to non-selective immunosuppressive properties [3].

Unexpected side effects that cannot be predicted from preclinical studies may occur when patients are first treated with a monoclonal antibody. In a recent phase I study healthy volunteers who were treated with TGN1412, a novel recombinantly expressed, humanised superagonist anti-CD28 monoclonal, developed serious multi-organ failure immediately after first administration. Intravenous infusion, of what was supposed to be a sub-clinical dose, of TGN1412 in the volunteers pro-

duced a sudden and rapid release of pro-inflammatory cytokines [1]. All six volunteers, who subsequently became critically ill, developed a severe cytokine release syndrome, including multi-organ failure. Although thankfully all survived, it is now becoming apparent that these volunteers may suffer long term disruption of their immune system including haematological malignancy. This not only emphasises the complex safety issues involved in protein drug development but the data obtained provides important insights into the natural course of the cytokine storm and the systemic inflammatory response syndrome (SIRS), without the background of another illness. It is currently unclear whether the severe effects of this type of cytokine release in humans is caused by the direct ligation of CD28 on T cells or by the ligation and activation of other cell types, leading to the release of tumour necrosis factor-alpha (TNF-alpha), further triggering the immunological cascade [1].

All TGN1412 volunteers initially had clinical signs that fit the criteria for SIRS. They then developed respiratory distress and pulmonary infiltrates, accompanied by renal impairment and profound disseminated intravascular coagulation. This pattern of organ impairment may be consistent with a generalised multi-organ response to inflammation or critical illness. However, the presence of pro-inflammatory cytokines (interferon-gamma and tumour necrosis TNF-alpha), would also suggest immune-mediated injury that is specific to the lung [1]. It is evident



⇒ Figure 1: The 3D structure of human IFNβ

nonetheless that the application of drugs that modulate co-stimulatory molecules will certainly need a more fundamental insight in how the diverse immunological actions of these pathways are organised.

Another striking example of unexpected adverse effects took place in the clinical trial programme using natalizumab. Natalizumab and interferon-beta (IFN β) are examples of two different classes of molecules that have found their place in the treatment armory of multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system. After one year of Phase III clinical trials, natalizumab was approved by the FDA for use in relapsing MS but was withdrawn three months later, due to three reported cases of progressive multifocal leukoencephalopathy (PML). In the so-called AFFIRM clinical trial (enrolment of 942 subjects with relapsing MS), natalizumab alone was shown to reduce the relapse rate and lesions, without causing PML [4]. After more than two years of combined natalizumab and IFN β -1a therapy, in the SENTINEL study (enrolment of 1196 relapsing MS patients), this combination was also shown to reduce the relapse rates and lesions compared with patients on IFN β monotherapy. However, two cases of PML occurred [3]. PML is an often fatal opportunistic infection of the central nervous system for which there is no specific therapy. It is caused by reactivation of a latent JC polyomavirus infection. An assessment of all trial patients who had taken natalizumab for one to two years (approximately 3000), showed the incidence of PML to be 1/1000 [5].

During both AFFIRM and SENTINEL, persistent antibodies to natalizumab developed in 6% of patients. These patients had an increase in infusion-related adverse events and a loss of efficacy of natalizumab [2, 4]. No drug-related anaphylactic or anaphylactoid reactions occurred in the SENTINEL study [2]. But during the AFFIRM trial [4], a total of 4% of patients in the natalizumab-treated group experienced hypersensitivity reactions. The patients who received additional standard pharmacotherapy for hypersensitivity

reactions were given either, oral or intravenous, antihistamines and/or corticosteroids and all fully recovered [6].

Safety, tolerability and immunogenicity of beta interferons

Three IFN β products – IFN β -1b (Betaseron), IFN β -1a (Avonex) and IFN β -1a (Rebif) have demonstrated beneficial effects in the treatment of patients with relapsing MS. IFN β is the first-line treatment of relapsing MS, and several phase III pivotal trials have shown efficacy in reducing exacerbations, slowing disability progression and reducing disease activity as measured with magnetic resonance imaging [7-9].

IFN β -1b is produced by recombinant DNA technology using *E coli*. It differs from natural human and recombinant IFN β -1a (made in Chinese hamster ovary cells) in having 165 amino acids (lacking methionine at position 1), a serine residue at position 17 to prevent incorrect disulphide bond formation, and no glycosylation of the asparagine residue at position 80. There are no obvious differences between IFN β -1b and IFN β -1a in their biological activity or *in vivo* pharmacokinetics. The main adverse effects of IFN β are local injection site reactions, flu-like symptoms and hyperthermia at onset. There is no drug hypersensitivity but each is associated with the development of neutralising antibodies (NABs).

A number of studies have demonstrated that the presence of neutralising antibodies causes a reduction in IFN β bioavailability as measured by reduced levels of bioactivity markers. Moreover, there is evidence suggesting that (persistent) NABs reduce therapeutic efficacy of IFN β in multiple sclerosis patients [10]. A recent Danish study suggests that neutralising antibodies against IFN β tend to persist long after the discontinuation of IFN β therapy [11, 12]. The clinical impact of these persisting NABs is unknown. Although recent *in vitro* work suggests that high-titer NABs to IFN β may block endogenous IFN β function and alter the chemokine/cytokine microenvironment within the central nervous

system, thereby modulating the profile and course of the local inflammatory response [13]. It has also been found that knock-out mice in which the IFN β gene is inactivated show a prolonged and more severe course of experimental autoimmune encephalomyelitis and a higher sensitivity for allergic inflammatory reactions [12]. Thus patients with continuing high levels of antibodies to IFN β may be more susceptible to some forms of immune-mediated disease, such as viral and opportunistic infections. It is reassuring, however, that despite extensive, long-term usage of IFN β , such problems have not been observed so far and that IFN β usage has not been associated with an increased occurrence of infectious disease [12].

Conclusions

Biopharmaceuticals can give rise to multiple, sometimes unpredictable, biological effects. Monoclonal antibodies provide the unique capacity to specifically target cell-surface molecules, thereby ablating cell lines or blocking ligand-receptor interactions. On the one hand, these agents can induce unique and robust therapeutic efficacy but, on the other hand, they can give rise to toxicity, either through their planned mechanism of action, through unexpected mechanisms of action, or through the induction of neutralising antibodies which can suppress efficacy and/or induce specific side-effects, including hypersensitivity reactions. Therefore, the long term impact of neutralising antibodies should be studied further.

Authors

Both authors participate in NABINMS, a specific targeted research project on neutralising antibodies to interferon-beta in multiple sclerosis, established by the European Commission under its 6th Framework Programme (www.nabinms.eu).

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Natalizumab: a new treatment for multiple sclerosis

Professor Hans-Peter Hartung, MD; Professor Bernd C Kieseier, MD

Natalizumab is thought to have a disease-modifying action resulting in a prolonged decrease of lymphocytes in the cerebrospinal fluid (it appears to impair immune surveillance of the CNS). This exciting development is set against an alarming safety profile.

Introduction

Multiple sclerosis (MS) is considered a prototype inflammatory autoimmune disorder of the central nervous system (CNS). Affecting some two million people worldwide, it interferes with activities of daily living, causes significant impairment and disability, and represents a major problem to the patients, their families and caregivers and the health system. The aetiology of this disease remains unknown, but an interplay between as-yet unidentified environmental factors and susceptibility genes appears to pave the way for a misguided immune response to molecular structures on the myelin sheath and axolemma (outer membrane). Most likely in the wake of an infective illness that renders autoreactive T-cells activated, a cascade is triggered in the CNS that results in demyelination, oligodendrocyte death, axonal damage, gliosis, and neurodegeneration [1].

In order to mediate a local immune response within the CNS, activated immunocompetent cells need to cross an anatomically tight interface that separates the systemic immune compartment from the nervous tissue, the blood–brain barrier (BBB). This mechanism of transendothelial migration is a multi-step process occurring in an ordered sequential fashion. In the first step, cellular adhesion molecules (CAMs) are expressed on the leukocytes and the vascular endothelium, resulting in slowing and attachment of the circulating leukocytes along the vessel wall (descriptively called “tethering” and “rolling”) [2]. The flowing blood quickly dislodges cells that touch the vessel wall, thus adhesion molecules act as mechanical

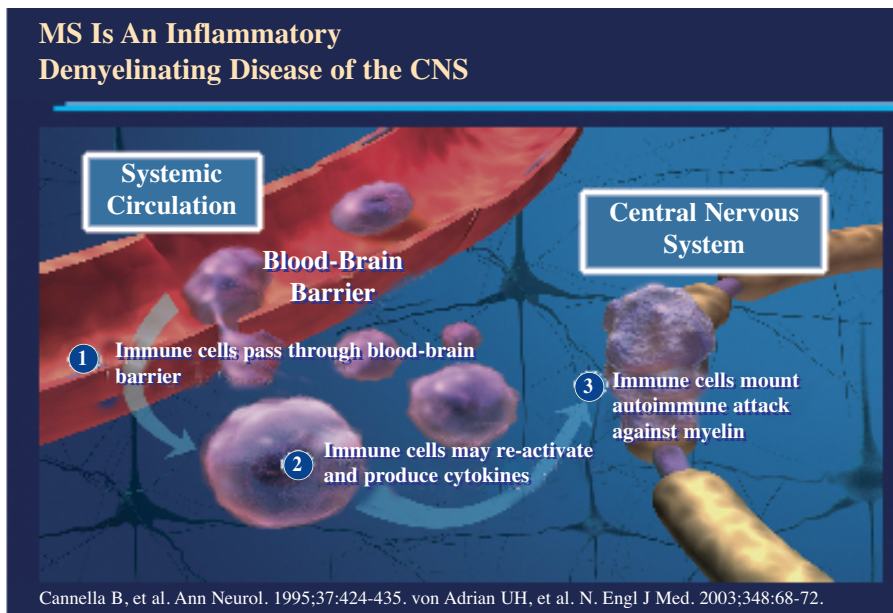
anchors, but also function as tissue-specific recognition molecules. Based on structural differences, CAMs can be categorised into four groups—the immunoglobulin “superfamily”, selectins, integrins, and cadherins—all of which are involved in lymphocyte recruitment and extravasation. The specific functions of individual CAMs have been elucidated by blocking their action with specific monoclonal antibodies in various animal models or by generating knockout animals for the corresponding gene of a particular CAM. The extravasation of leukocytes into the CNS parenchyma is facilitated by the expression of CAMs on both leukocytes and cerebral vascular endothelial cells. The latter display various CAMs, of which two—vascular adhesion molecule-1 (VCAM-1) and E-selectin—are expressed only on activated endothelial cells. The

extravasation receptor on leukocytes is very late antigen-4 (VLA-4) [2, 3].

An assessment of natalizumab

Natalizumab is a monoclonal humanised antibody (MAb) that targets the $\alpha 4\beta 1$ -integrin (VLA-4) on the surface of leukocytes. It was designed to prevent the immigration into, and accumulation within the CNS of, encephalitogenic white blood cells [3]. Additional mechanisms impacting T cell reactivation and B cell proliferation are also conceivable [4, 5].

Since a previous phase II proof-of-concept study suggested remarkable clinical efficacy [6] two phase III trials on natalizumab in MS were initiated and recently published [7, 8]. In the AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis) trial natali-



Cannella B, et al. Ann Neurol. 1995;37:424-435. von Adrian UH, et al. N. Engl J Med. 2003;348:68-72.

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zumab was applied as a monotherapy (300 mg IV or placebo every 28 days for up to 28 months) in 942 MS patients who had not received any immunotherapy in the preceding six months. 96% of subjects in the treatment arm were devoid of new Gd-enhancing lesions compared to 68% in the placebo group, as studied by MRI-imaging. Relapse frequency was reduced by approximately two-thirds over years one and two and natalizumab also significantly delayed disease progression. The SENTINEL (Safety and Efficacy of Natalizumab in Combination with Interferon beta-1a in Patients with Relapsing Remitting Multiple Sclerosis) study tested the combination of natalizumab with IFN β -1a IM once-weekly against IFN β -1a alone. Subjects on IFN β -1a were randomised to either natalizumab 300 mg (n=589) or placebo (n=582) infusions every 28 days. Individuals receiving combination therapy had a reduced relapse rate, 54% fewer relapses compared with IFN β -1a alone and significantly fewer MRI observed lesions. Frequent adverse events in both studies comprised anaphylactoid reactions, rash, arthralgia and headache.

Based on the positive interim analysis of both these phase III trials, natalizumab was approved by the FDA for the treatment of "relapsing forms of MS" in November 2004. However, in February 2005, the substance was withdrawn from the market because two patients receiving natalizumab in combination with IFN β -1a developed progressive multifocal leukoencephalopathy (PML), a lethal infection of the CNS with JC virus [9-11].

As a consequence, an extensive re-examination of all patients who had received natalizumab was performed considering various safety aspects [12]. Taken together, no additional cases of PML were identified in more than 3,000 patients exposed to the medication. Based on these results the FDA approved an application for resumed marketing of natalizumab as monotherapy in patients with "relapsing forms of MS who have not responded adequately to, or cannot tolerate other treat-

ments" in June 2006. To minimise the risk of further serious adverse events, a special restricted distribution programme and the risk management plan TOUCH (Tysabri Outreach Unified Commitment to Health) were introduced in the US (see www.FDA.gov). In Europe, natalizumab has been approved by the EMEA as monotherapy for (i) patients with high disease activity despite sufficient treatment with IFN β as well as for (ii) patients with initially high disease activity. In several EU countries reimbursement for the drug has been granted, e.g. Denmark, France, Germany, Greece, Italy, the Netherlands, Sweden and Switzerland. Austria and Spain are pending. England (NICE) and Scotland (SMC) took a more reserved position for this new drug in the absence of long-term favourable outcome data.

Conclusion

The advent of natalizumab for the treatment of MS opens a new era of immune-specific therapy. However, the current situation is unique since the high efficacy of this MAb is opposed by an uncertain safety profile, especially in long-term application. Natalizumab interferes with a critical step in MS disease pathogenesis, which is the entry of encephalitogenic T cells into the CNS compartment. Owing to its mechanism of action, the substance may impede immune surveillance of the CNS. It is not known, however, whether reactivation of the JC virus (or a de novo infection) was caused by general immunosuppression, or by a more specific effect related to the particular mechanisms of drug action [13]. Balancing the risk to benefit ratio of this class of agents, it is necessary to learn much more about JC virus infections without delay [14].

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A comprehensive risk management plan when administering natalizumab

Professor Ralf Gold, MD

Ralf Linker, MD



This article points the reader to a risk management algorithm, originally developed by the manufacturer and now published, that should be followed when natalizumab is prescribed. Patient Alert Cards are available.

Natalizumab (Tysabri) is a recombinant humanized IgG4 monoclonal antibody produced in murine myeloma cells. It binds to the $\alpha 4$ -subunit of $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins expressed on the surface of all leukocytes except neutrophils, and inhibits the $\alpha 4$ -mediated adhesion of leukocytes to their counter-receptors [1, 2]. This binding reduces migration of activated inflammatory cells, including T-lymphocytes, from the vasculature into, for example, the brain parenchyma. This is a central mechanism by which it is thought that natalizumab manages to reduce plaque formation and relapse rates in patients with multiple sclerosis (MS). Two-year placebo controlled clinical trials in this indication have shown monthly infusions of natalizumab reduced MS relapse rates by over 60% and were associated with a concomitant reduction in neurological disability [3]. These effects are almost double those seen with currently available therapies. Therefore natalizumab was licensed in the US and Europe in June 2006 for patients with relapsing-remitting MS and high disease activity.

During the development of the drug individual cases of progressive multi-

focal leukoencephalopathy (PML) were unexpectedly reported [4] in patients receiving combination therapy with natalizumab and IFN- β . PML is a disease usually associated with states of severe immunosuppression, either in cancer treatment, HIV infection or immunosuppression in transplant recipients. PML is caused by reactivation and infection of the brain by a normally dormant virus, JCV, which is found in more than 80% of healthy individuals. It is a serious disease, which usually results in death or severe disability and for which there is currently no specific treatment. In patients with AIDS developing this disease immune reconstitution by the use of highly active anti-HIV drugs has been found to improve outcome. Currently there is no good explanation for the development of PML during treatment with natalizumab [5]; a meticulous evaluation of patients from the MS studies showed no further cases of PML [6]. The occurrence of PML in patients treated with natalizumab has led to the development of a risk management plan (RMP) associated with the marketing approval of the drug designed to ensure the greatest benefit-risk ratio for individual MS patients treated with natalizumab.

The European RMP for natalizumab describes a programme to further investigate and minimise the risk of PML and other known and potential risks of treatment. As part of the plan a series of studies will be performed to define better the mechanisms underlying the development of PML, to define the exact incidence of its occurrence, to determine any particular at-risk patient groups and to describe the overall safety profile of natalizumab during marketing use. A large patient observational study (TYGRIS), to be performed partly in Europe, is one of the mainstays of this series of studies but the plan also describes other clinical and preclinical studies investigating further effects of natalizumab which may be relevant for its effects on PML.

The RMP also aims to reduce known risks of treatment with the drug. The risk minimisation plan in Europe involves physician educational material for neurologists prescribing natalizumab and Patient Alert Cards distributed to patients prescribed the drug.

The physician educational material describes the patient population suitable for treatment with natalizumab. This

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| <ul style="list-style-type: none"> ➤ Show this card to any doctor involved with your treatment, not only to your neurologist ➤ See the TYSABRI patient information leaflet for more information ➤ Keep this card with you for 6 months after the last dose of TYSABRI, since side effects may occur even after you have stopped treatment with TYSABRI <p>Patient's Name _____</p> <p>Doctor's Name _____</p> <p>Doctor's Phone _____</p> | <p>TYSABRI is a registered trademark of Elan Pharma International Ltd. in various countries</p> <p>Biogen Idec™ is a trademark of Biogen Idec.</p> <p>© 2006 Biogen Idec Code: XXXXX</p> | <h2 style="margin: 0;">Patient Alert Card</h2> |
|--|--|--|

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include patients previously treated with interferons but whose clinical response was inadequate as well as untreated patients with particularly aggressive forms of MS. Before start of treatment a baseline MRI should be done which can be used to assist with interpretation of future MRIs in case of difficulties in differentiating MS relapse or PML if new neurological symptoms and signs occur. An important risk-minimising feature is that patients should not be immunocompromised whilst receiving natalizumab as it is known that immunosuppression is a risk factor in itself for development of PML. To this end no immunosuppressant or immunomodulator drugs (including interferons) should be used in patients receiving natalizumab. In patients who have previously taken immunosuppressants, physicians should ensure that the patient is immunocompetent before prescribing natalizumab. A special working group has recently published guidance [7] for prescribing physicians to assist with this assessment. Both a time window between stopping previous immunotherapy and a baseline immune status are part of these guidelines.

A large part of the physician educational material covers the management of new neurological signs and symptoms in patients with MS treated with natalizumab to assist with the differentiation of MS relapse and to assess possible early evidence of the development of PML. An algorithm has been written which describes a step-by-step procedure to be followed. The features covered include symptoms and signs typical of PML and MS relapses and MRI findings indicative of PML or MS plaques. If PML cannot be excluded physicians are

required by the algorithm to perform cerebrospinal fluid examination for the presence of JCV, which would indicate PML rather than MS relapse. During investigation to exclude PML natalizumab infusions should not be given but once PML is excluded treatment can recommence. These algorithms have now been published [8] to assist with the dissemination of this information.

The physician educational pack also requires a raised response to other opportunistic infections including determination of the infecting organism if serious infections develop and monitoring of patients for hypersensitivity reactions during infusions. Up to 6% of patients in the initial studies developed neutralising antibodies, and this was often associated with allergic reactions. In Europe independent, centralised test laboratories have been established in each country.

A Patient Alert Card will be provided for patients prescribed natalizumab. This is similar to alert cards given to patients prescribed anti-TNF products in EU. The alert card describes the symptoms that patients should be aware might indicate infection and about which, if they are persistent or severe, they should seek advice from their prescribing physician. In addition specific indicators of cognitive deterioration are described, as such changes are often associated with early PML and are a distinguishing feature from MS neurological relapse. To this end it is recommended that patients also give the alert card to a carer or family member as they may be more sensitive to changes in cognition, about which the patients themselves may be unaware.

Use of this enhanced information for physicians and patients, if PML or other serious unusual or opportunistic infections do occur, means they can be detected early and natalizumab treatment stopped. Therefore this risk can be minimised. In the meantime further information concerning the mechanisms by which natalizumab increases predisposition to developing PML, specific risk factors, further investigations into the management of PML and possible new treatment regimens will all be investigated as part of the risk management plan. As new information becomes available the risk minimisation activities will be adapted. Based on theoretical considerations, rapid removal of natalizumab via plasma exchange procedures should also support immediate reconstitution of the immune system.

Tysabri represents an important new therapeutic option for patients with MS. Despite the risk of developing severe diseases such as PML, the magnitude of efficacy in preventing progression of MS, demonstrated in the clinical trials, is such that the European Medicines Agency considered the risk / benefit balance of treatment with the drug positive and approved the product for use in a subgroup of patients. The risk minimisation activities associated with the drug should reduce risk to the minimum currently possible and as our understanding improves further reductions may become possible. At this point it may be possible for the patient population considered suitable for treatment to be broadened so that more patients suffering from a disease as disabling as MS can be offered the benefits of this treatment, which are undoubtedly greater than those of other established therapies [9].

TYSABRI® Patient Alert Card

This alert card contains important safety information that you need to be aware of before you are given TYSABRI and during treatment with TYSABRI.

Prior to treatment with TYSABRI

- You should not be treated with TYSABRI if you have a serious problem with your immune system
- You should not take any other long-term medicines for your multiple sclerosis while receiving TYSABRI

During treatment with TYSABRI

There have been reports of a rare brain infection called PML (progressive multifocal leukoencephalopathy) that have occurred in patients who have been given TYSABRI. PML usually leads to severe disability or death.

- The symptoms of PML may be similar to an MS (multiple sclerosis) relapse. Therefore, if you believe your MS (multiple sclerosis) is getting worse or if you notice any new symptoms, it is important that you speak to your doctor as soon as possible.

- Discuss your treatment with your partner or caregivers. They might see new symptoms that you might not notice.

Serious infections may occur with TYSABRI. Speak to your doctor as soon as possible if you think you have an infection, and show this card and the package leaflet to them. The symptoms of infections include:

- an unexplained fever
- severe diarrhoea
- shortness of breath
- prolonged dizziness
- headache
- stiff neck
- weight loss
- listlessness

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The practicalities of administering natalizumab and patient management including hyper-sensitivity reactions

Lisa Costelloe, MRCPI; Professor Michael Hutchinson, MD, FRCP

The efficacy of natalizumab in the treatment of severe relapsing multiple sclerosis (MS) is indisputable and offers new hope to MS sufferers worldwide. However, it should only be administered to the appropriate patient, in a suitable setting, and with rigorous monitoring protocols in place.

Introduction

Natalizumab is the first in a class of disease modifying therapies (DMTs) known as selective adhesion molecule (SAM) inhibitors and acts by preventing the specific inflammatory events leading to the development of multiple sclerosis (MS) lesions. Endothelial cells on the lumen of blood vessels express vascular cell adhesion molecule-1 (VCAM-1) at sites of active MS lesions. VCAM-1 is bound by $\alpha_4 \beta_1$ -integrin (also known as very late antigen-4), an adhesion molecule found at high levels on the surface of all leukocytes except neutrophils. The interaction between VCAM-1 and $\alpha_4 \beta_1$ -integrin is required for leukocyte adhesion, firm attachment, and transmigration across the blood-brain barrier into the CNS. Natalizumab, a recombinant, humanised antibody, binds to $\alpha_4 \beta_1$ -integrin and blocks its interaction with VCAM-1. As a result, leukocyte migration into brain tissue is inhibited, reducing inflammation and preventing the formation of lesions [1].

Natalizumab represents the first targeted immunotherapy for use in MS patients and has recently been licensed for use in highly active relapsing remitting MS. This group consists of those patients who have clinical and radiological evidence of rapidly evolving central inflammation, as well as those who have evidence of ongoing disease activity despite treatment with standard immunomodulatory agents such as β -interferon. Since this drug has only recently been introduced clinically in a selected group of MS patients, most of our practice guide-



lines for use of the agent come from the AFFIRM study. Two-year data from this study demonstrated a 68% reduction in the relapse rate compared to placebo, and in fact 28% of treated patients

the end of the follow-up period. Thus, natalizumab is currently the most effective biologic agent available for the treatment of relapsing MS. However, in early studies of the agent in combination with other immunomodulatory agents for both MS and Crohn's disease, three cases of progressive multifocal leucoencephalopathy (PML) were detected, two of which proved fatal [3, 4, 5]. It is therefore with cautious optimism that the drug is reintroduced in the clinical setting.

A natalizumab infusion service and patient treatment

In the EU, prescribing is limited to physicians experienced in the treatment of neurological diseases and with timely access to MRI, in facilities that are prepared to deal with any hypersensitivity reactions. Education directed to physicians covers guidance on the appropriate patient population for treatment, algorithms for managing suspected cases of opportunistic infections, including PML, and information on other risks. Prescribers and patients must understand the risks of treatment with natalizumab, including PML and other opportunistic infections. An MRI scan should be obtained prior to treatment to help differentiate future MS symptoms from PML.

All patients previously treated with other immunomodulatory therapies must undergo a "wash-out" period before commencing natalizumab.

remained free from all clinical and radiological evidence of disease activity at

Administration of natalizumab is restricted to infusion centres where the staff

members have been educated about risks and appropriate use. During monthly infusion visits, members of the medical staff have regular opportunities to screen for early symptoms of PML and other opportunistic infections.

Natalizumab comes as a concentrated solution to be diluted and infused intravenously at a dose of 300 mg over one hour. It is given once every four weeks and α_4 -integrin receptor saturation is maintained for 28 days after each infusion [6]. The relative benefits and risks of natalizumab therapy for a particular patient will depend on disease severity, treatment history and any other factors that could compromise the patient's immune system. Risk minimisation is achieved by promoting informed benefit–risk decisions, ensuring that natalizumab is not prescribed to immunocompromised patients, and maintaining vigilance for other opportunistic infections, including PML and other adverse events.

Once the infusion service is introduced, unit staff will require training and patient and family members will require counselling; patient education materials should be available. Measures must be instituted to ensure ongoing liaison with pharmacy and the general practitioner, regular monitoring of all equipment and systems should be put in place to ascertain that protocols are followed and documentation completed.

Hypersensitivity reactions

As with all biologic agents, hypersensitivity reactions are observed in a proportion of treated patients. In the AFFIRM study, twenty-five (4%) of the treated patients experienced 27 hypersensitivity reactions (see Table 1). The majority of these consisted merely of urticaria, and anaphylactic/anaphylactoid reactions occurred in <1% of treated patients. Fifteen of the 27 hypersensitivity reactions had occurred by the second infusion, and an additional eight occurred between the third and seventh infusions [7]. Life-threatening hypersensitivity reactions that have been observed with

Table 1: Hypersensitivity reactions in the AFFIRM study [2, 5]

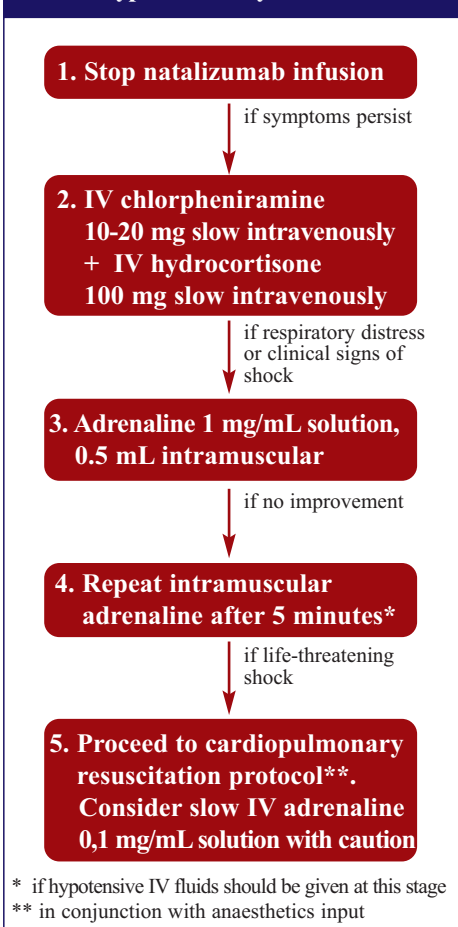
| No. of hypersensitivity reactions | 27 |
|--------------------------------------|----|
| Non-serious reactions | 20 |
| Urticaria or generalised urticaria | 13 |
| Allergic dermatitis | 2 |
| Hypersensitivity | 5 |
| Serious reactions | 8 |
| Urticaria | 1 |
| Hypersensitivity | 2 |
| Anaphylactic/anaphylactoid reactions | 5 |

other monoclonal antibodies such as rituximab [8] have to date not been associated with natalizumab. All natalizumab patients who have had hypersensitivity reactions to date have recovered fully without evidence of cardiopulmonary compromise. Management of infusion reactions is at the discretion of the treating physician. The patient is observed during and for one hour after natalizumab administration and the infusion is immediately discontinued upon the first signs or symptoms of a hypersensitivity reaction. If a hypersensitivity reaction develops, the standard practice of initially using oral or intravenous antihistamines and corticosteroids is employed (see Table 2: Treatment algorithm). Equipment for cardiopulmonary resuscitation including adrenaline must always be readily accessible for use by appropriately trained personnel if needed. Patients who develop hypersensitivity reactions must discontinue treatment with natalizumab; further infusions run the risk of severe anaphylactoid reaction.

Immunogenicity

Like many other protein therapeutic agents, natalizumab is potentially immunogenic; in both the AFFIRM and SENTINEL studies persistent neutralising antibodies (NABs) developed in 6% of natalizumab-treated patients. There are two consequences of persistent NABs; there is a loss of efficacy of the drug and a higher risk of hypersensitivity reactions. Patients with a persistently positive antibody status must permanently discontinue dosing with the agent. It is suggested that patients should be tested for the presence of persistent antibodies

Table 2: Treatment algorithm for serious hypersensitivity reactions



if after six months of treatment their disease activity is not reduced.

Opportunistic infections including PML

As with the use of all immunosuppressant agents, vigilance for the development of opportunistic infections in natalizumab-treated patients is of paramount importance. To date, the development of serious opportunistic infections including PML in natalizumab-treated patients has occurred in the context of concurrent use of immunosuppressive therapy or immunosuppression. For this reason all patients previously treated with other immunosuppressive therapies must undergo a “wash-out” period before commencing natalizumab. However, the possibility that natalizumab alone may cause PML or other serious infections cannot

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be excluded. Therefore, all treated patients presenting with symptoms suggestive of PML should be investigated promptly. It is also important that natalizumab treatment be administered under the care discontinued while PML is ruled out by MRI and CSF examination.

Conclusions

Natalizumab represents decades of scientific research come to fruition. Its efficacy in the treatment of severe relapsing MS is indisputable, and this therapy offers new hope to MS sufferers worldwide. However, it should only be administered to the appropriate patient, in a suitable setting, and with rigorous monitoring protocols in place. Clinically, we have a responsibility to be proficient at both the recognition and management of hypersensitivity and immunogenicity to the agent in the short term, as well as

being vigilant for the development of serious infection including PML in the longer term.

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