

A practical Approach to immunomodulatory therapy of MS

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I. Introduction:

In Multiple Sclerosis (MS) neither the pathogenesis of the disease nor the mechanism of an action of immunomodulating therapies (IMT'S) are fully understood [1,2,3]. Genetic predispositions, socioeconomic influences, gender (females: males = 2:1), infectious agents, and other environmental factors have been implicated [4,5]. Identifying treatment has been challenging since the discovery of a successful therapy usually begins with a solid understanding the pathogenesis of the disease. In spite of a lack of complete understanding of the pathogenesis, four immunomodulating and one immunosuppressive drug have received FDA approval for the treatment of MS since 1993.

This chapter provides a current overview of the definition and pathogenesis of the disease, the different types of MS, a new diagnostic criteria, the rationale for early therapy, a review of the approved MS therapies, the strategies to evaluate ongoing treatment efficacy, the management of "sub optimal" treatment responders and the prospects for future therapies. (Table 1)

The emphasis is on relapsing remitting MS (RRMS) because most of the therapeutic data deals with RRMS. No immunomodulating therapies (IMT's) have been FDA approved for primary progressive MS (PPMS) or secondary progressive MS (SPMS) without relapses.

One immunosuppressive, antineoplastic agent, mitoxantrone (Novantrone), also has FDA approval for "worsening MS". Its role as a "rescue therapy" of sub optimal responders to the IMT's will also be discussed.

Table 1

MS and Immunomodulating therapies (IMT's)

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II. The Definition and Pathogenesis of MS: A reappraisal

The traditional definition of Relapsing Remitting Multiple Sclerosis (RRMS) has stated “MS is a relapsing remitting disease of central nervous system myelin secondary to a T-cell mediated inflammatory process”. While the definition is partially accurate, newer research findings indicate the disease is much more complex. The following is a re-analysis of the definition based on recent data concerning the clinical and pathological processes in RRMS.

1. “A Relapsing-remitting Disease Course.....”

This concept is only partially correct. Clinically, MS first appears as a relapsing and remitting disease course in 80-85% of patients. After an exacerbation, clinical recovery of all or partial function is likely. This recovery is followed by clinical stability until the next exacerbation. However, between relapses the MRI demonstrates ongoing dynamic changes, even when clinical worsening is not obvious [6]. As many as ten new MRI lesions are seen for each new clinical relapse. These new MRI events may last from a few weeks to months or may result in permanent MRI lesions such as increasing T2 burden of disease or “black holes”. In addition, most patients initially presenting as relapsing-remitting MS transition to secondary progressive MS (SPMS) after 10 years [7,8]. In other words, most people with RRMS will end up with SPMS without treatment, even if they are “normal” between early attacks. Therefore, the concept of “relapsing-remitting” is misleading because of continued MRI damage and the transition to SPMS in most patients.

Other clinical types of MS include Primary Progressive MS (PPMS) and progressive relapsing MS (PRMS) [9]. Primary Progressive MS accounts for 10-15% of all MS patients and usually occurs after age 40. The clinical course is best characterized as steadily progressive disability beginning in the lower extremities without acute attacks [10]. The spinal cord is the primary target and MRI's may show little evidence of acute inflammation. Progressive relapsing MS (PRMS) is uncommon (<5% of MS patients) and follows a progressive course with occasional interspersed attacks.

Benign MS accounts for 10-25% of RRMS patients [11]. The diagnosis of benign MS is difficult prospectively because many young people seem to fit the benign criteria yet

transition to progressive disease (SPMS) after several years. Benign MS is characterized by infrequent, mild attacks with primarily sensory symptoms and little or no long term disability. The “benign” diagnosis is only confirmed after 15-25 years. Unfortunately, if the “benign” condition transitions to SPMS, the opportunity to treat effectively is diminished. Early damage, which might have been prevented with treatment, is not likely to be reversible. For example, patients on placebo for 2-3 years in clinical trials did not “catch up” to the therapeutic benefits of patients treated from the onset [12]. What is lost early appears to be lost forever.

2. “A disease of myelin.....”

Myelin damage has been the hallmark of MS pathology. However, newer data indicates that, while myelin is one target of the immune system dysfunction, oligodendroglia cells (myelin producing cells), axons and neurons can also be damaged [13,14,15,16,17,18]. This damage can be dramatic, occur early in the disease, lead to permanent disability and may account for the cognitive dysfunction seen in over 50% of MS patients. In fact, cognitive dysfunction may not closely correlate with motor dysfunction such as walking and balance problems. A more accurate MS definition would not restrict the disease to “damage of myelin”, but would include damage to several components of the central nervous system.

3. “A disease secondary to T-cell mediated inflammation process....”

The immunopathogenesis of MS is undergoing intense scrutiny. Do T-cells really initiate the damage in all (or any) types of MS? Do antibodies play any role in MS damage? Is MS only one disease?

New research indicates four distinct types of immunopathology [19]. Type I involves activated T-cells, macrophage and cytokine mediated multifocal damage of myelin. This pathological description was thought to be the major pathology in MS. However, recent data suggest that less than half of MS patients demonstrate this pathology. Type II involves B cells (antibody) and complement mediated multifocal damage. Type III is a more diffuse low grade inflammation with loss of myelin associated glycoprotein (MAG) and apoptosis of oligodendrocytes (versus myelin). Type IV appears to involve degeneration (non inflammation induced) of oligodendroglia cells. In summary, T cell mediated damage predominates in only Type I. Further, the 4 types may be mutually exclusive, i.e. if a patient has one type of pathology; the other 3 types are not present. If these observations withstand scientific scrutiny, MS would not be regarded a single disease entity. Instead, a syndrome with four distinct pathogenic mechanisms would be a more accurate definition. This also implies that different treatments may be needed for different types of MS. This diverse pathology may help explain the diversity of therapeutic responses to IMT's.

Other leading MS authorities have evidence that the initial destructive event in MS may be oligodendroglia cell death, which is unrelated to inflammation [20]. In this case, inflammation may be a response to damage and not the cause of CNS damage. If correct, this model might drastically change our treatment approach. In any event, recent pathological data may lead the way to more targeted treatments resulting in even better outcomes.

III. New diagnostic criteria for early MS: Implications for therapy

In spite of the challenges to the definition and pathological understanding of MS, certain observations are apparent. First, IMT's can modify the disease course in RRMS. Second, early RRMS treatments produce more favorable outcomes compared to delayed therapy. Furthermore, data demonstrate that IMT's initiated after the first neurological events are associated with a prolongation of time to the next episode and "clinical Definite MS" as well as a reduction of MRI lesions [21,22]. Therefore, the trend is to treat before the second clinical neurological episode if the MRI indicates ongoing activity, after other illnesses are excluded. In fact, a new MS diagnostic criterion has been adopted to take advantage of earlier diagnosis and treatments [23].

The McDonald Criteria for the diagnosis of MS incorporates MRI findings and other tests into an earlier MS diagnosis [23]. For example, if an initial event or Clinically Isolated Syndrome (CIS) is associated with an abnormal MRI and if a follow-up MRI after 3 months shows new lesions, a diagnosis of RRMS may be established before the occurrence of a second clinical episode.

IV. The rationale for early treatment

As stated above, favorable outcomes are seen with early treatment, while delaying treatment has less favorable outcomes [12,24]. For example, IMT's in patients with SPMS who no longer have acute attacks are unlikely to delay the progression of disability [25]. This lack of IMT's benefit on disease progression comes at a time when the treatments may still have a positive effect on the inflammatory process by MRI measurements and reduction of exacerbations. In other words, a vigorous IMT anti-inflammation response in early RRMS reduces attacks and delays disease progression whereas IMT's in later SPMS may reduce inflammation but have little effect on disease progression. Why? [26]

One theory may help explain this data. While inflammation is robust early in RRMS, a degenerative process which is non-inflammatory predominates later. Since this later degeneration or apoptosis process is not mediated by acute inflammation, IMT's are unlikely to be beneficial. The mechanism producing degeneration is unclear and no treatment has been demonstrated to be very adequate in this degenerative process.

However, a link between early inflammation and later degeneration is plausible. For example, early in MS, when inflammation is prominent, many cells are damaged but may not be destroyed. These cells may recover and/or other adjacent cells may expand their capacity to remyelinate axons. Consequently, patient's recover from their acute attack after weeks or months. These repaired but distressed cells may function well initially but may be programmed to die earlier than if they were not distressed. Therefore, these cells may only live for 5, 10, or 20 years before apoptosis occurs. Since their eventual cell death is not immediately related to acute inflammation, IMT's at that later time would have no effect. However, if IMT's effectively reduced inflammation and subsequent early damage, the cell would not have become distressed and programmed to die early in the disease course.

Therefore, early anti-inflammatory IMT may help prevent the degeneration/apoptosis seen later if they reduce the number of CNS cells damaged in the

first place. The American Academy of Neurology, the MS Council for Clinical Practice Guidelines and the National MS Society all support early treatment with IMT's [27,28].

V. Immunomodulating therapeutic options for MS:

Since 1993 four IMT's and one immunosuppressive agent have received FDA approval for the treatment of MS. Three of the IMT's (Betaseron, Avonex and Rebif) fall in the class of interferon betas while the fourth, glatiramer acetate (G.A.) (Copaxone), is a polypeptide comprised of four randomly sequenced amino acids. A detailed review of these drugs is beyond the scope of this chapter, which focuses on the practical considerations with each of the treatments. In addition the emphasis is on an Evidence Based Medicine approach regarding Class I clinical trial data as reviewed by independent investigators, i.e., not sponsored by the pharmaceutical industry [28,29,30].

Defining Class I scientific trials requires a careful analysis of the methodology [28]. Class I trials must be randomized, prospective, and adequately controlled. Patients need not be blinded to treatment modalities, but the evaluating clinicians should not be aware of the treatment status of the patients. The American Academy of Neurology and the MS Council have conducted an evidence based medicine review of the four IMT's based on their pivotal trial data and other Class I scientific studies. In addition, two Cochrane Review Committees have conducted independent evidence based medicine reviews using Meta analysis of the interferons and glatiramer acetate data [17,30]. This chapter attempts to summarize those independent evaluations along with Class I Head to Head clinical trials to aid in the understanding of each drug's role in MS therapy.

Mechanisms of Action

The mechanisms of action of the immunomodulating therapies are not fully understood. However, interferon betas have a number of actions that are beneficial in MS. They include reduction of pro-inflammatory cytokines such as gamma interferon, increase secretion of anti-inflammatory cytokine such as interleukin 10, increase suppressive T-cell activity while prohibiting the proliferation of lymphocytes, the down regulation of antigen presentation crucial for the activation of lymphocytes, and the inhibition of lymphocyte trafficking through the blood brain barrier to the CNS [26]. G.A. binds to major histocompatibility complex class II molecules and creates competition with MPB which promotes the transformation of TH-1 lymphocytes (producer of pro-inflammatory cytokines) to TH-2 lymphocytes (producer of anti-inflammatory cytokines) in the peripheral blood. Glatiramer acetate specific cells also appear to have positive effects within the brain parenchyma as well including expression of IL-10, TGF Beta and brain derived neurotrophic factor [31].

Interferon β 1b (Betaseron /Betaferon)

In 1993 Interferon β 1b became the first FDA approved IMT for Multiple Sclerosis. The standard dose is 250 mcg every other day subcutaneously. The initial pivotal trial in RRMS demonstrated a 33% reduction in the overall relapse rate and 50% reduction in moderate to severe relapses [32,33]. The MRI data revealed a dramatic (83%) reduction in gadolinium (GAD) enhanced lesions. In addition there was a reduction in

total T-2 lesion burden by MRI at 2 year [34]. A trend toward reduction in progression of disease was not statistically significant.

The second Class I study with Interferon β 1b involved secondary progressive MS (SPMS) [35,36]. The drug increased the time to confirmed disability and to wheelchair while decreasing exacerbation rates, MRI lesions, hospitalization, and steroid use. A second Class I study in SPMS demonstrated the drugs effectiveness in reducing relapses and MRI lesions but did not demonstrate an effect on disease progression [25]. These contrasting results are best explained by the fact that the first study was done in early SPMS where the second study was done in later SPMS. These findings re-enforce the concept that earlier treatment is more likely to be effective than later treatment in delaying disability.

Based on these two studies of SPMS, the FDA has approved the use of Interferon β 1b in “relapsing forms” of MS which would include early SPMS when patients are still having relapses.

Interferon β 1b for RRMS was evaluated in Italy in an independent (no pharmaceutical company sponsor) Head to Head trial vs. weekly Interferon β 1a (Avonex 30 mcg per week) [37,38]. This trial (INCOMIN) was rated as Class I for MRI outcomes but only Class III study for clinical parameters since the physicians evaluating the clinical outcomes were not blinded. Both clinical and MRI outcomes demonstrate a clinically significant benefit of Interferon β 1b over Interferon β 1a in the 2 year study. The MRI parameters were approximately 50% different, while the clinical parameters were between 35-50% different, all favoring Interferon β 1b. This trial supported the previous AAN/MS Council recommendation of a probable dose response effect with higher dosed Interferon Beta being more effective than lower dosed drug [28].

The newest data of MS Interferon β 1b efficacy are intriguing. Two recent studies indicate that increasing the dose of Interferon β 1b is well tolerated and has a further positive effect on the MRI [39,40]. Potentially, this indicates that interferons may be more effective at an even higher dose. A Class I clinical trial is currently underway comparing double dose Interferon β 1b vs. the standard dose. A third arm of this trial is comparison with Copaxone since there has never been a Class I study comparing the effects of interferons vs. Copaxone.

Initially, one of the biggest practical issues with Interferon β 1b was lack of tolerability. Flu-like side effects were common and skin reaction, including occasional skin necrosis, prevented many patients from continuing therapy [32]. Fortunately, with changes in treatment protocols (dose escalation and prophylactic ibuprofen or acetaminophen), the use of auto-injectors and targeted nurse support systems, the drop-out rate for Interferon β 1b due to side effects is only about 5% in the first year of therapy [41].

Interferon β 1a (Avonex)

Weekly, 30mcg, intramuscular Interferon β 1a was approved by the FDA in 1996 for the reduction of relapses as well as progression of disability in RRMS versus placebo [42]. In addition, there was a 50% reduction in GAD enhanced MRI activity. There was no statistically significant difference in T2 lesion burden on MRI. A subsequent Class I study which doubled the dose of Interferon β 1a weekly did not show increased efficacy. These results support a statement by the AAN/MS Council guidelines that suggest that

increasing the frequency (as well as dose) of interferon beta injections may also be important.

In a study of MS patients with Clinical Isolated Syndrome treated with weekly Interferon β 1a versus placebo, a significant delay was found in the time to a second relapse (clinical definite MS) and a reduction of MRI lesion with Interferon β 1a [21].

In a Class I trial in SPMS Interferon β 1a weekly did not prolong the time to progression of disability utilizing the standardized expanded disability status scale (EDSS) [43]. However, using the MS Functional Composite Scale (MSFCS) a difference from placebo was noted in one of the three sub scales, i.e. the 9 hole peg test [44]. However, no significant difference was found compared to placebo on the cognitive test or the ambulation index. Weekly Interferon β 1a has not been FDA approved for the treatment of SPMS.

The side effect profile of weekly Interferon β 1a intramuscularly is similar to the other interferons, although skin reactions are less frequent because of the intramuscular injection. Neutralizing antibodies are least likely with weekly Interferon β 1a versus the other interferons [45].

Weekly Interferon β 1a has been evaluated in two Head to Head trials versus higher dosed, more frequently administered Interferon betas. INCOMIN with Interferon β 1b versus β 1a has been reviewed. A second Head to Head Trial also compared weekly Interferon β 1a versus 3 times weekly subcutaneous Interferon β 1a (Rebif). This Class I trial (EVIDENCE) demonstrated that the higher dosed, more frequently administered Interferon β 1a (Rebif) was clinically superior on MRI and on the percentage of relapse free patients over a 24 week period. The trial was extended to 48 weeks and the clinical superiority was maintained.

Interferon β 1a (Rebif)

Based on the above described EVIDENCE Trial [46] and the pivotal trial (PRISMS), Interferon β 1a given 44 mcg 3 times per week subcutaneously was approved by the FDA for relapsing-remitting MS in 2002. The PRISMS study was the first pivotal trial of any IMT that demonstrated over a two year period a favorable impact on all four of the study outcomes which are viewed by neurologists as most important, i.e. reduced relapse rate, prolonged time to progression of disability, reduction of T2 burden of disease on MRI and reduction of gadolinium enhanced lesions on MRI. Four year and eight year results were also positive [47,48]. Also, a randomized study in CIS and early RRMS showed a delay to clinically definite MS (time to next relapse) and reduced MRI lesions compared to placebo (ETOMS) [22]. A follow up from the pivotal trial in RRMS has shown continuing benefit of therapy up to 8 years in RRMS patients still on high dose Interferon β 1a therapy.

A Class I clinical trial of high dose Interferon β 1a in SPMS did not demonstrate a difference in prolonging time to progression of disability by the EDSS scale (SPECTRIMS) [49]. However, a reduction in relapse rate and MRI activity were noted. A post hoc analysis which categorized patients with or without relapses did show a favorable effect on prolonged time to progression of disability in patients with relapses versus patients without relapses in this SPMS study. However, the FDA has not approved Interferon β 1a for the SPMS.

The side effect profile is similar to Interferon β 1b except that some people report more burning at the subcutaneous injection site with Interferon β 1a [50]. As with Interferon β 1b, newer treatment protocols (dose escalation and prophylactic ibuprofen or acetaminophen) reduce the flu-like side effects. The immunogenicity of high dose Interferon β 1a is greater than low dose weekly Interferon β 1a but less than with Interferon β 1b. Again the clinical significance of NAb's is uncertain.

Neutralizing Antibody

Neutralizing antibodies to Interferon β 1b range from 25-45% of treated patients. The relevance of this finding is discussed later. The production of neutralizing antibodies (NAb's) to interferon betas and their clinical relevance is hotly disputed [45,51,52,53]. The data on NAb's is conflicting and the AAN/MS Council concluded that the utility of measuring NAb's is uncertain. NAb's have not been shown to effect progression of disability, although there is mixed data on MRI and relapse rates. Most of this data is not Class I. Also NAb's are often transient. One study surveyed sub-optimal responders to Interferon β 1b and found only 7% of these patients had high levels of neutralizing antibody and about 80% of suboptimal responders had no detectable neutralizing antibody. In the Italian Head to Head Trial (INCOMIN) of Interferon β 1b versus Interferon β 1a, no effects of NAb's on either clinical or MRI outcomes were found [37,54]. In the pivotal trial of weekly Interferon β 1a, no significant difference was found in clinical outcomes of NAb+ vs. NAb- patients, although gadolinium MRI lesion were more numerous (but not significant) in NAb+ patients. However, NAb+ patients had a slightly lower relapse rate (but not significantly different). No change in EDSS was noted between the two groups [55]

In the author's opinion, if a patient is doing well clinically and by MRI, but is NAb positive, the patient should continue on interferon. On the other hand, if a patient were responding sub-optimally, even if no NAb's are found, a change in therapeutic regimen should be considered. Emphasizing the patient's clinical response to therapy and not the results of a controversial test seems prudent at the present time. Therefore, the author does not utilize NAb testing.

An overview of interferon beta therapy

Interferon betas have similar mechanism of actions and similar side effects depending on route of administration. All can be associated with hematologic and liver function abnormalities and are all rated as Class C for safety in pregnancy. None are recommended for women who are pregnant or are contemplating pregnancy in the near future. Fortunately, women who have become pregnant while on interferons have not demonstrated an increase risk of fetal abnormalities. However, interferons have been shown to be abortifacient in animal studies. Regular blood work for liver function abnormalities and hematological abnormalities are recommended. Significant abnormalities may necessitate lowering the dose, a drug holiday, or discontinuation of therapy. Depression may be seen with any of the interferons. However, MS patients have an increased risk of depression even without therapy. Nonetheless patients who are depressed should be treated before the initiation of interferon therapy and if a depression develops during IMT therapy, an evaluation of the potential role of IMT's are indicated and discontinuation of therapy may be justified.

A major differentiating factor in Interferon β 1a therapy is efficacy. The higher dose more frequently administered interferons (Betaseron & Rebif) have been demonstrated to be more effective than weekly Avonex in two Class I Head to Head Trials. The two high dose interferons are more immunogenic, i.e. higher NAb's, than the lower weekly Interferon β 1a but the clinical relevance is uncertain. Another difference is that Interferon β 1a's are available in a pre-filled syringe, but must to be refrigerated, and may cause injection site burning. Interferon β 1b must be mixed with the diluent before injection, but does not require refrigeration, and does not have the frequency of injection site pain compared to subcutaneously administered Interferon β 1a.

Glatiramer acetate (Copaxone)

Glatiramer acetate (GA), 20 mg daily, given subcutaneously in a pre-filled syringe (refrigeration required) is FDA approved for the treatment of relapsing-remitting MS based on a pivotal trial which showed a reduction of relapse rate compared to placebo [56]. There was no difference in EDSS scores in the two groups and an MRI component was not done. A subsequent Class I MRI study did demonstrate a positive effect on the MRI [57].

No Class I studies of secondary progressive MS have been published using glatiramer acetate. A recently completed Class I study of GA vs. placebo in Primary Progressive MS was discontinued because of apparent lack of efficacy of therapy. On further analysis, some effect of GA in males with PPMS was noted. In any event, the FDA has not approved GA for the treatment of either PPMS or SPMS. A Class I, placebo controlled trial of oral glatiramer acetate did not demonstrate efficacy.

GA. is generally well tolerated with a majority of patients having only a mild skin reaction. One study showed a high incidence of dimpling of the skin secondary to loss of fatty tissue (lipoatrophy) in females on GA. Also 15% of patients in the pivotal trial had a brief systemic reaction to at least one injection of GA. Patients experienced chest tightness, flushing, palpitation, and anxiety lasting for a few minutes but no serious long term sequelae were seen. The etiology of the reactions is unknown but patients need to be warned. No routine blood work is required for patients on GA. A major issues with GA is its lack of Class I data to indicate effect on progression of disability.

Neutralizing Antibodies to GA have not been identified. Almost all patients on Glatiramer acetate produce antibodies. One study suggests that some of these antibodies have a deleterious effect on efficacy [58]. However, other studies have not shown this to be the case [59] and some have postulated the antigen antibody complex formed by the GA may be part of the positive therapeutic effect of the drug [60]. Conflicts about NABs abound. Commercial tests for antibodies to GA are not available.

Long Term Effects of Immunomodulating Therapy

No scientifically robust studies have been conducted on the long term effectiveness of IMT's. Most of the Class I studies have been limited to 2 years. However, long term follow-up data of patients on therapy are encouraging. Long term studies indicate that patients on Interferon β 1b for 12 years actually have an improvement of T2 burden of disease from baseline. Glatiramer acetate patients treated for 10 years have relatively stable relapse rates and show little progression of disability. High dose Interferon β 1a 8 year follow-up data is also positive, as is data on low dose weekly Interferon β 1a in 5 years. The problem with interpretation of this data is that patients who stay on therapy

may be a sub population of “responders” or patients who would have a benign disease course without therapy. None of these long term data provides insight to the superiority of one product over another. Nonetheless, newly diagnosed patients may find it encouraging to know that other patients on therapy for over 10 years are still doing well.

Immunomodulating Therapy effect on cognition

The initial Interferon β 1b trial demonstrated a positive effect on some cognitive tests in patients on Interferon β 1b vs. placebo [61]. The pivotal trial of weekly Interferon β 1a showed positive effects on cognitive outcomes [62]. One study with glatiramer acetate did not show a positive effect on cognition [63]. However, these results are not sufficient to favor one drug over another. However, it may reassure patients to know that some data indicates IMT's have a beneficial effect on cognition. Future Head to Head trials are comparing efficacy of therapy on cognition. At that time drug comparisons may be more meaningful.

VI. Practical evaluation of effectiveness of immunomodulating therapies

While the four IMT's have FDA approval for Relapsing Remitting MS, differences exist in efficacy and in individual responses to the various therapies. All treatments are only partially effective. Patients may respond better to one drug vs. another drug. However, measuring a suboptimal therapeutic response is imprecise [64]. Setting rigid criteria for defining a suboptimal response may not be appropriate for an individual patient.

For example, assume a patient had 2 moderate exacerbations of MS within one year. Is this suboptimal response? If a patient has had five exacerbations the previous year, we may consider this a reasonable response to therapy and continue the patient on the treatment. However, if the patient had no attacks on therapy for four years and then had two moderate attacks in one year, most physicians would consider this a suboptimal response and consider changing their treatment regimen.

For another example, assume that three new MRI lesions in 1 year is adopted as a criteria for suboptimal response. However, if a patient had 10 new MRI lesions the year before treatment and now only has 3 new MRI lesions in the last year, would this be suboptimal response? By contrast, if the patient had no new MRI lesion for 3 years while on therapy and now has developed 3 new MRI lesions, most physicians would be concerned.

One practical approach to defining a suboptimal response is to establish individual caution signs for individual patients. Looking for increasing clinical disease activity is the most reliable determination is suboptimal response. No increase in exacerbations and no progression of disease are ideal. In addition, some physicians get yearly or bi-yearly MRI's to help evaluate for suboptimal response. However, a consensus conference of MS experts did not recommend the routine use MRI's to evaluate therapeutic efficacy. They recommended MRI's only if the physician is contemplating a change in therapy. In spite of this recommendation, many treating physicians use the MRI in their ongoing evaluation of efficacy of therapy. Some treating physicians use NAb testing as a measure of suboptimal response. However, the American Academy of Neurology/MS Council guidelines state that the utility of measuring neutralizing antibodies is uncertain [28].

VII. Managing suboptimal treatment responders

If a patient is determined to be suboptimal responder to an IMT therapy, increasing the dose or switching therapies is appropriate. For example, if the patient is on low dose weekly Interferon β 1a, switching to a higher dose interferon is reasonable. Switching to GA is another alternative. Another approach might be to add additional treatments although no Class I scientific evidence exists for this approach. Pulse steroids [65], azathioprine and methotrexate are potential add on therapies.

In Suboptimal responders to interferons switching to Copaxone or adding an additional therapy are appropriate. Also, suboptimal responders on Interferon β 1b may benefit by increasing the dose by 50-100%, based on recently presented data [40,54].

The use of Mitoxantrone (Novantrone) is appropriate in patients who have suboptimal responses [66]. Mitoxantrone is an anthracenedione derivative, anti neoplastic agent which is approved by the FDA for worsening MS (RRMS & SPMS). It kills T-cells, B-cells and macrophages while enhancing suppressive T-cell functions, inducing apoptosis of antigen presenting cells and decreasing both pro-inflammatory and anti inflammatory cytokines [67]. The standard dose is 12 mg per meter squared every three months intravenously up to a maximum of 140 mg per meter squared. Although scientific long term studies are lacking, many MS experts add Mitoxantrone to the current IMT's. Patients tolerate this combination well. The issues with Mitoxantrone include a blue tint to the skin and sclera, amenorrhea which may be permanent, increase risk of infections, cardiotoxicity, and a remote chance of an increased risk of leukemia. Amenorrhea and cardiotoxicity are the most immediate potential problems. Although most patients do not get permanent amenorrhea, this potential risk should be explained to the patient. Cardiotoxicity is evaluated by measuring the left ventricle injection fraction. If reduced, Mitoxantrone should be discontinued. Cardiotoxicity may be irreversible and precipitate heart failure.

VII. Future Therapies

A number of potential MS therapies are undergoing clinical trials currently, Antegren, IVIG, Campath, Cladribine, T-cell vaccination, and perphenidone. The most likely to be approved soon is Antegren [68].

Antegren is an alpha-4 integrin in the class of selective adhesion molecules (SAM) inhibitors. It binds to integrin on T cells to prevent adhesion to the Blood Brain Barrier endothelial cells and subsequent migration of these cells into the brain parenchyma. A short term phase 2 study has shown a reduction of attacks and MRI lesions vs. placebo [69]. A recent company press release on a phase III trial with one year data indicates a 66% reduction of relapse rate compared to placebo in RRMS.

Summary

Immunomodulating therapy has made marked improvements in the lives of many MS patients over the last 11 years. While these treatments are only partially effective and their use must be continued to maintain maximum effectiveness, they have improved the disease course, improved care and stimulated research which will ultimately result in new treatments which are likely to be even more effective. All of the treatments have side effects, most of which can be prevented or managed. Recent scientific reviews and studies

have begun to differentiate efficacy between the therapies. Efficacy has taken on new importance, since new data reveals the disease is much more complex with early (often sub-clinical) damage that may lead to both short and long term negative consequences. The emphases on early treatment with the most efficacious therapies are a reflection on new research findings. However, focusing on IMT's alone is focusing on lymphocytes rather than the patient. IMT's are not substitutes for caring health care providers, symptom management, and aggressive rehabilitation in the integrated care of MS patients.

Conclusion: A practical approach to selecting IMT's for Patients.

As a result of new data the treatment emphasis has become heavily weighted to treating early and aggressively. Several factors have led to this change including the complex and progressive nature of the disease, the propensity of RRMS to transition to SPMS after several years, the finding that damaged brain early in the disease course does not recover (What is lost is gone forever!), the availability of 4 IMT's, and the scientific and independent reviews of IMT's. No longer are neurologists waiting until the disease progresses to moderate or severe disability to initiate treatment. In fact, new diagnostic criteria encourage treatment before a second episode.

The choice of treatment is a balance between efficacy, tolerability and convenience. Tolerability is becoming less of an issue. For example, Interferon β 1b lack of tolerability was a major deterrent a few years ago. Now, with new techniques and protocols only 5% of people can not tolerate Interferon β 1b. Convenience is a relative issue. A more effective but less convenient drug may keep more people from being hospitalized for attacks or ending up in a wheelchair.

Therefore, a major factor in treatment decisions is efficacy. Fortunately all four IMT's are FDA approved based on scientifically valid clinical trials. However, these two year studies may not tell the whole story. The goal is reducing long term disease stability, for which no treatment has any scientifically valid data. Therefore experience with the drugs long term becomes an important additional factor. Integrating evidence based medicine reviews with long term experience provides an optimal background to treat with a drug that is most likely best for an individual patient.

Utilizing evidenced based medicine reviews (AAN/MS Council and Cochrane Review), interferons have demonstrated the most robust data to show that they decrease progression of disability. The two Class I Head to Head trials of interferons support the AAN/MS Council recommendation that higher dosed (and likely more frequently administered) interferons are probably more effective than the lower dose weekly interferon. However, in clinical practice many patients seem to be doing well on all IMT's. All drugs have some long term, but not scientifically robust, data that indicate that people who stay on "their drug" are doing well after several years. In fact each drug has responders and sub optimal responders among a population of MS patients. The factors determining response to IMT begins with dose and efficacy data, but may also include the type of immunopathology, genetic factors, the underlying course of MS, the patients' compliance or as yet to be determined factors.

Could patients who respond to a drug with less robust efficacy data in Class I trials do even better if they were switched? The data on patients who switch therapy is limited [38]. Many questions remain unanswered.

For the present, the physician is best served by understanding the conclusions of independent reviews and scientific head to head trials and then putting these recommendations into perspective with his and MS experts' experience. The practice of telling patients to make their own decisions after reviewing drug companies infomercial video tapes is discouraged. The treating physician's responsibility is to educate the patient to his/her best ability and separate marketing spin from evidence based medicine review.

Close communication between the physician, the care team, the patient and the families provides for the most successful long term management of MS.

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