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Immunosuppression: Promises and failures

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Abstract

The author participated very early in the use of immunosuppressors in the treatment of multiple sclerosis. He reviews evidence which support their use. IV Methylprednisolone, azathioprine and mitoxantrone are supported in their use by evidence of a level appropriate to the date of their generation while Cyclosporine A and Cyclophosphamide are not. The author also reviews the benefits and side effects of each of these medications, insisting on a practical approach to their use. The author concludes that since immunomodulators have been approved, the use of the immunosuppressors has been reduced, however there is a strong possibility that their use will be rekindled in association with immunomodulatory medications.

Keywords: Multiple sclerosis; Immunosuppression; Clinical trials; Corticosteroids; Azathioprine; Mitoxantrone; Cyclophosphamide; Metotrexate

1. Introduction

Few therapies have demonstrated effectiveness in multiple sclerosis and immunosuppressors (IS) are among them. Further, IS have been used for over 40 years, a witness to their safety. Most of them have originally been used as anti-inflammatory medications in small open trials until large-scale double blind randomized placebo-controlled trials became the essence of evidence-based medicine. This review will summarize our knowledge as of the present time and we all know time is a limitation as trial techniques and the availability of evidence evolve.

We are going to review their efficacy, their side-effects and how they are used in different parts of the world. We will stress how these medications have been losing a large portion of its market through the Evidence Based Medicine phase. We will then evaluate how some of these medications have a chance of showing a rebound in their popularity in association with other drugs. We will limit our review to Methylprednisolone, Azathioprine, Cyclophosphamide, Cyclosporine and Mitoxantrone.

1.1. Methylprednisolone

Intravenously doses of 500–1000 mg has been demonstrated to result in short-term benefits. [1] Milligan et al. in a double blind randomized placebo controlled trial (DBPCCT) showed that IVMP (500 mg) was of benefit to decrease clinical disability at week 1 and week 4 when patients were in relapse. There was also benefit at 4 weeks in chronic (secondary progressive) patients essentially due to improved spasticity. Methylprednisolone appears now to be the established treatment for acute relapses (Cochrane review) [2] when doses of 1000 mg are used for 3 to 5 days. Oral and IV routes seem to be equivalent if used at the same high dose [3]. Steroids have a clear effect on the Blood Brain Barrier in MS and clearly reduce the number of gadolinium enhancing lesions for 2 to 6 weeks.

The results of the optic neuritis treatment trial [4] comparing oral prednisone (50 mg/day) and IVMP indicated a benefit on vision at 2 years. A post-hoc review of the data showed reduced risk of developing MS at 2 years in patients treated with Methylprednisolone. This had disappeared at 5 years. It is the reading of this author however that this would lead to using IVMP for all optic neuritis. The evidence that long-term cyclical use of IVMP treatment can alter the course of MS is scant Whitham and Bourdette [5] as well Zivadinov

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R. et al. [6]. Side effects of short course high dose steroids include rise in blood pressure, rare arrhythmias, hypomania, insomnia and acute psychosis. An acute chemical hepatitis is rare and liver enzymes are occasionally increased. Treating patients having an infection should be avoided. Risks are cumulative and become a concern when monthly pulses are considered to treat rapidly progressive cases. In this case preference might be to Mitoxantrone (see below).

1.2. Azathioprine

An imidazolyl derivative of 6 mercaptopurine is generally used in transplantation. Has been used empirically in the treatment of multiple sclerosis since the early 60s, mostly in Europe, pioneered in France by Aimard [7], in Lyon, and Sabouraud [8] in Rennes. The first DBRPC trial was that of Milanese et al. [9] in which AZA treated patients did better. This was not confirmed by Ellison et al. in 1989 [10]. Eventhough the British and Dutch AZA trial group showed some minor benefit in patients who were treated, the differences were not significant [11]. There are suggestions that on discontinuing the drug, the disease can be reactivated and relapses can occur [12]. The use of AZA is still very high. AZA is generally used for RRMS, SPMS or as an add-on to Interferon Beta. Rarely used for rescue or aggressive MS [13,14]. It is a first choice among all the immunosuppressive regimens. France (12% of MS patients are treated with AZA) remains the greatest user while Canada uses AZA in less than 1.5% of the patients. Complications of Azathioprine use are multiple and can be serious including nausea, bloating on initiation of therapy with a rare idiosyncratic allergic hepatitis. Regular adjustment of dose on results of WBC should permit to avoid leucopenia and lymphopenia. Regular measurements of alkaline phosphatase should permit to avoid macro nodular cirrhosis with cholestasis and anasarca. The risk of cancer has been estimated at 1/800 patient years [15]. These risks have lead the British and Dutch investigators to conclude that although the results favor a small benefit from AZA it is so small in the face of the side effects that it is probably not worth the risk.

Studies are on going to evaluate AZA as a combination with Beta Interferon 1b [16].

1.3. Cyclosporine

Cyclosporine is a complex amino acid essentially used in transplantation but its use has spread to autoimmune disorders. It is difficult to interpret the study from Kappos et al. [17] who found no difference (Benefit) versus Azathioprine, however the North American study [18] demonstrated benefit of a single daily dose of Cyclosporine A given 2 years in a DBRPC. There was improvement in slowing time to becoming wheelchair bound, delay in loss of independence of upper extremities but had no effect on time to sustained progression. These benefits were however shadowed by a large proportion of drop outs (more so in the Cyclosporine group) and a number of side effects (nephrotoxicity, hypertension as well as gingival hyperplasia and hirsutism). Our experience in treating MG patients with cyclosporine indicates that monitoring blood levels of the drug is essential both to assess efficacy of absorption (cyclosporine has a very low and variable bioavailability and GE absorption) and avoid adverse side effects. Cyclosporine in the form of Neoral® taken in divided doses generates a better absorption and might be worth re-evaluating either in isolation or in association with Beta interferon.

1.4. Cyclophosphamide

Cyclophosphamide is an alkylating agent related to the nitrogen mustards. It is a powerful immunosuppressant acting as it cross-links DNA in actively multiplying cells. Used as a pulse by Gonsette and Demnty [19] it decreased relapse rate. It does not help during relapses [20].

The paper by Hauser et al. [21] reported an unblinded study of 58 MS patients with randomization in 3 groups; ACTH pulse only, ACTH pulse+high dose cyclophosphamide, ACTH pulse+low cyclophosphamide and plasma exchange. The high dose cyclophosphamide did much better than the ACTH only $p<.004$ and was not different from the ACTH+low cyclophosphamide+plasma exchange. The authors concluded that progressive MS could be stabilized by short-term intensive immunosuppression with cyclophosphamide pulse ACTH.

There has been a recent Cochrane review of Cyclophosphamide in MS [22]. The Cochrane Review could not achieve their goal due to the small number of RCTs available and the heterogeneity of treatment regimens. This did not allow definite conclusions. Only 2 trials [23] and [24] are informative: Likosky et al. was a placebo controlled, single blinded study of progressive MS of cyclophosphamide 500 mg/day 5 times. Outcome included EDSS, Ambulation Index and incapacity status. 42 patients were included. There was no difference found at 12, 18 and 24 months. The Canadian Cooperative study did not show any statistically significant effect of cyclophosphamide or plasma exchange.

These results are at odds with the original study of Weiner et al.

Despite these negative reports, the regimen recommended by Weiner and the Northeast Cooperative MS treatment group was further refined by adding pulses every other month for 2 years after a 2–3 weeks IV induction treatment.

It is now used for secondary progressive MS (albeit not approved) especially for patients with rapid progression. It is used in induction at 600 mg/m^2 daily for 5 days with IV Solu-medrol and is followed by monthly boosters adjusting the dose to WBC counts. The following recommendations have been made to adjust the dose of boosters of Cyclophosphamide to the WBC.

Before Cyclophosphamide infusion of 800 mg/m^2, WBC should be >4000/mm^3.

If 3000–4000, give 75% of dose.
If 2000–3000 give 50% of dose.
If <2000 skip the dose.

Then adjust next monthly dose on Nadir WBC.

WBC at Nadir	Action
1500 to 2000/mm^3	booster dose of 800 mg/m^2+1 g IV solumedrol
<1500/mm^3	decrease by 100–200 mg/m^2
>2200/mm^3	increase by 200 mg/m^2
<1500/mm^3	decrease by 100–200 mg/m^2

Boosters should be given 1 day per month for 12 months, at which time effects of therapy should be re-evaluated. If therapy works, give booster every 6 weeks for another year, and then every 2 months for a third year; the authors do not advise administering cyclophosphamide for more than 3 consecutive years.

Cyclophosphamide is presently used essentially in France and the US (in respectively 6.9 and 5.5% of the patients).

Canadians seem to be quite reluctant (0.6%) similarly to UK and Scandinavian neurologist.

There is further hope to stabilize aggressive MS in combining Cyclophosphamide with Interferons [25,26] or Rituximab [27].

1.5. Mitoxantrone

Is a synthetic anthacenedione derivative and is used as an anti-neoplastic. Mitoxantrone had been pioneered in pilot trials by Noseworthy et al. 1993 [28]. Bastianello et al. [29] did a small DBPC of low dose Mitoxantrone that suggested clinical and MRI efficacy. It is used IV at 12–20 mg/m^2 and has been shown to alter the course of rapidly worsening RRMS 28 or SPMS [30]. It induces macrophage medicated suppression of B-cells — T helper and T-cytotoxic lymphocytes. In the trial of Edan et al. [30] patients were treated with IV Solumedrol compared to IV Solumedrol+ Mitoxantrone 20 mg monthly for 6 months. The clinical part of the trial was not blinded but the MRI part was double blinded and there was a significant reduction in the gadolinium enhancing lesions. Results by Millefiorini et al. were confirmatory but less convincing [31]. In the MIMS trial of Hartung et al. [32] patients received Mitoxantrone in isolation at 12 mg/m^2 every 3 months for 2 years. Mitoxantrone was found to be significantly more effective than placebo in terms of clinical and MRI parameters. A composite index was used which had not been tested before and together with the fact that attacks were evaluated by the non-blinded physician resulted in the TTA subcommittee of the AAN following Goodin in his evaluation that this very well planned and executed trial had a low rating generating class III evidence [33]. The same committee also rated the Edan trial as class III for clinical evidence and class II for MRI evidence. The whole rating was improved by evidence generated by Millefiorini et al. [34] and by Bastianello et al. [35] despite the fact that these trials included only a small number of patients respectively 51 (27 on Mitoxantrone) and 25 (13 on Mitoxantrone). It is the reading of this reviewer that the Therapeutics and Trial assessment of the American Association of Neurology [33] despite its attempt at bringing objectivity has been unduly harsh on the evidence and we personally support the fact that Mitoxantrone is beneficial for rapidly progressive relapsing MS and SPMS on relapse rate disability and Gadolinium enhancement on MRI. If it is clear that similar to interferons, Mitoxantrone acts essentially on the inflammatory component of MS and not on the secondary degenerative process. However the major limitation to its use comes from the lifetime dose limitation at 140 mg/m^2 due to cardiotoxicity.

Indeed, side effects are a major limitation in the use of this drug. Some 5% of the patients complain of nausea, alopecia, UTI, amenorrhea, leucopenia and elevated liver enzymes. Nausea, alopecia, leucopenia and liver dysfunction respond well to cessation of the drug. Few patients however can remain amenorrheic, they are generally older. There have been 5 reports of Acute Myeloblastic leukemia occurring between 3 months and 5 years after treatment. As it is difficult to know exactly how many MS patients have been treated, it is difficult to evaluate the risk with any degree of confidence. Patients certainly need to be informed of this deathly risk. We generally recommend handing out a written informed consent to discuss with their family and reflect upon before starting treatment.

Cardiotoxicity is a complication common to long-term anthacoid therapy. It appears to be dose related and has been shown to appear above 160 mg/m^2. Patients should be monitored for left ventricular ejection fraction. LVEF was reduced to <50% in 3–4% of Mitoxantrone treated patients in the MIMS trial versus 0 in placebo. Data reported by Ghalie and Edan on 2000 patients indicated no heart failure and out of 12 patients whose LVEF went <50% only 3 did not recover [36,37].

Our routine is to give Mitoxantrone 20 mg/m^2 together with IV Solumedrol if there is no infection, no leucopenia and if LVEF is >50%. We repeat this monthly for 3 months and if the LVEF remains >50% we repeat this quarterly for 18 months. Obviously one then gets close to the dose limit and indicates the limitation in the use of this medication. We are eagerly awaiting results of trials where Mitoxantrone and interferon Beta 1b are used sequentially as it is quite probable that this will reinforce the effect of Interferons and possibly reduce the incidence of Neutralizing antibodies in Interferon treated patients.

According to Hommes and Weiner, neurologists are voting with their prescription pads and the use of Mitoxantrone – an FDA approved drug for MS – has now spread, more so in Europe (2.5 to 6.9%) than in North America (.5 to 1%). It is recommended for rapidly evolving MS patients "who have failed other drugs" i.e. it is probably seen as being indicated after interferons have failed. Personally this reviewer would see it as a possible alternative in high NAB positive interferon failure patients who have failed therapy. We would also

recommend following the criteria used by Edan which include the presence of Gadolinium enhancing lesions.

Other chemotherapeutic agents are being tested including Paclitaxel with promising results. Cladribine which after 3 trials in progressive MS is now being tested by Serono in relapsing MS. These compounds have the clear advantage of being taken orally. Mycophenolate is being tested in combination with Interferon Beta-1b. FTY720 which inhibits lymphocyte marginalization has shown efficacy in a phase II trial. It is reported as deflecting lymphocytes from their target by pulling them out of the circulation and trapping them in lymphatic organs.

It is difficult to assess if monoclonal antibodies can qualify as immunosuppressants, however, they are being extensively tested in MS: including Campath (antiCDW52) showed promising effect on MRI lesions but no effect on progression. Natazilumab (antiVLA-4) has been shown to reduce relapses by 60% as well as MRI lesions. It has been approved by FDA but rapidly withdrawn because of association with PML in 3 treated patients. The FDA has requested a risk management plan to authorize its re-introduction (March 2006). This totally unexpected side effect occurred only in association with Interferon or immunosuppressants. In March 2006 FDA experts approved the re-introduction of Tysabri® accompanied by a risk management plan. Rituximab (antiCD20) is now being tested in a phase III trial.

2. Is the future in associating therapies?

It is a well known medical strategy to associate medications having different modes of action and different toxicity profiles, hoping that their therapeutic effects will be additive and their side effects will not. In this register a number of physicians have chosen, without much evidence to support their choice, to treat breakthrough disease in Interferon treated patients with the addition of an immunosuppressor. An alternative approach consists in using an induction phase as G. Edan's trial of Mitoxantrone for 6 months followed by Beta-Interferon. Numerous open attempts to associate immunosuppressors and different medications have been started by individual physicians but, as of this date, only five trials are registered with the NIH and are on-going [38].

3. Conclusion

Immunosuppressants can be used safely if proper attention is given to their side effects. They are active on the inflammatory phase of MS, however the evidence is relatively limited, most probably for historical reasons. It is for the same historical reasons that MRI evidence of their activity is weak or lacking. There are some distinct reasons why they could be prescribed: Some of them have been used for more than 40 years which bodes well for their safety and most are much less costly than interferons. Their future, however probably lies in the possibility of using them in association with disease modifying drugs.

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