

# Remission of Multiple Sclerosis Post-Liver Transplantation

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**ABSTRACT: Background:** The effect of liver transplantation on pre-existing multiple sclerosis (MS) has never been reported. We report the three year post-transplant neurological outcome of a patient with MS. **Case report:** A Caucasian woman with MS received an urgent liver transplant for fulminant liver failure at the age of 59. Her Extended Disability Scale Score (EDSS) pretransplant was 5.0 and clinically she had cerebellar and brainstem dysfunction. Post-transplant immunosuppression consisted of tacrolimus, mycophenolate mofetil and tapering corticosteroids that were discontinued after 1.5 years. Post-transplant her EDSS decreased to 2.0 and after three years she is clinically asymptomatic with only very mild dysarthria on neurologic examination. Long-term maintenance immunosuppression consists of low dose tacrolimus. **Conclusions:** Combination immunosuppression with tacrolimus may have a beneficial effect on MS although an effect of donor allograft itself can not be excluded.

**RÉSUMÉ: Rémission de la sclérose en plaques après une transplantation hépatique. Introduction:** L'effet de la transplantation hépatique sur une sclérose en plaques (SEP) préexistante n'a jamais été rapporté. Nous rapportons le suivi neurologique d'une patiente atteinte de SEP ayant subi une transplantation hépatique trois ans auparavant. **Cas clinique :** Une femme caucasienne atteinte de SEP a reçu une transplantation hépatique en urgence pour une insuffisance hépatique fulminante à l'âge de 59 ans. Son score à l'échelle de Kurtzke, Extended Disability Scale Score (EDSS), avant la transplantation était de 5,0 et elle avait des signes cliniques de dysfonction cérébelleuse et tronculaire. Elle a reçu du tacrolimus, du mofétilmycophénolate et des corticostéroïdes à dose décroissante sur une période de 1,5 ans comme immunosuppresseurs après la transplantation. Son EDSS a baissé à 2,0 après la transplantation et elle est asymptotique au point de vue clinique trois ans plus tard. À l'examen neurologique, elle ne présente qu'une légère dysarthrie. Elle ne reçoit que du tacrolimus à faible dose comme immunosuppresseur à long terme. **Conclusions :** Bien qu'un effet de l'allogreffe elle-même ne puisse être exclus, une combinaison d'immunosuppresseurs incluant le tacrolimus pourrait avoir un effet bénéfique sur la SEP.

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We report the course of multiple sclerosis (MS) in a patient treated with tacrolimus, mycophenolate mofetil and tapering prednisone for three years post-liver transplantation for fulminant hepatic failure. To date the effect of solid organ transplantation on MS has not been reported in the literature. There is also little published experience with the immunosuppressive medications used and the efficacy of such combination immunosuppression in MS is unknown.

## CASE REPORT

The patient, a Caucasian female, who is currently 62-years-old, presented with the onset of relapsing-remitting MS at the age of 57. She had three relapses during the first year after initial presentation, including cerebellar and brainstem dysfunction. She reached an Extended Disability Scale Score (EDSS) of 5.0 after the third episode, within nine months of initial symptoms. The EDSS score of 5.0 was persistent for seven months with clinical findings of left gaze palsy, cerebellar dysarthria, nystagmus and cerebellar ataxia. Her MRI revealed white matter lesions consistent with demyelination.

Cerebrospinal fluid analysis revealed an immunoglobulin (Ig)G: albumin index of 0.89 [normal: 0.34-0.66], an IgG synthesis rate of 10.2 mg/d [normal < 3.4 mg/d] and oligoclonal bands. Subjectively, her quality of life was reported to have significantly deteriorated as a result of her MS symptoms. A trial of interferon beta-1a was interrupted after seven weeks by the development of fulminant liver failure, as previously reported,<sup>1</sup> requiring emergent liver transplantation. Her post-transplant immunosuppression (Table) consisted of delayed, lower dose (due to hepato-renal syndrome) tacrolimus (Prograf; Fujisawa Canada Inc, Markham ON), mycophenolate mofetil (Cellcept; Hoffman-LaRoche Canada Inc, Mississauga ON), and tapering prednisone. Her

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postoperative period was complicated by cytomegalovirus infection and acute rejection reaction.

She has not had any relapses of MS during the three years since transplantation and has very mild residual dysarthria and ataxia. Symptomatically she felt that the majority of her neurological symptoms had resolved by six months post-transplant and that she was virtually free of neurologic complaints by nine months post-transplant. Because of post-transplant complications specific to her liver transplant, it was difficult for her to distinguish mild MS symptoms from the post-transplant symptoms. Her EDSS decreased from 5.0 to 2.0 (mild residual intermittent dysarthria) within two months post-transplant and has remained unchanged between 1.0 and 2.0 throughout the post-transplant period; the burden of disease on MRI remained unchanged (143 mm<sup>2</sup> before transplantation to 113 mm<sup>2</sup> 18 months post-transplant). The neurologic examination three years post-transplant is without neurologic findings other than the very mild dysarthria. She is currently maintained on low dose tacrolimus and azathioprine with normal allograft and renal function and reports that her quality of life has returned to the pre-MS state.

## DISCUSSION

Our patient with significant pretransplant disability from MS has experienced a remarkable recovery post-transplant despite suffering from early medical complications associated with the transplant process. To date there is a void in the reported experience of outcomes in patients with MS undergoing solid organ transplantation and this report is the only one so far that reports on long-term neurological outcomes. From a solid organ transplant perspective, there is a tremendous discrepancy between the great number of patients in need of a solid organ transplant and the limited availability of donor organs creating a philosophy that allocation of scarce organs should be given to

those with the best possible outcomes. An important aspect of our report lies in the fact that co-existing significant medical conditions, including MS, may be considered contra-indications to transplantation unless reports to the contrary are published.

In terms of immunosuppression (Table), our patient received an induction pulse of methylprednisolone at the time of graft implantation and a second pulse for the treatment of acute graft rejection. Maintenance oral glucocorticoids, however, were low dose and tapered over 18 months. Although studies of glucocorticoid therapy have reported benefit in short-term outcomes with high-dose pulse corticosteroids in reducing progression in patients with multiple sclerosis<sup>2</sup> and longer term benefit with cyclic high dose pulse corticosteroids,<sup>3</sup> it is difficult to attribute our patient's long-term favourable outcome to the transplant corticosteroid regimen alone. The cornerstone of all transplant immunosuppressive protocols is the calcineurin inhibitor class of immunosuppressive agents (i.e. tacrolimus, cyclosporine) which can be associated with a wide spectrum of neurotoxicity, including mild to fulminant leukoencephalopathy.<sup>4,5</sup> Moderate or severe CNS toxicity is reported in a substantial number of patients treated with tacrolimus after orthotopic liver transplantation (21.3%) and cyclosporine (11.7%).<sup>6</sup> Lesion location in cyclosporine and tacrolimus neurotoxicity may include only white matter lesions or mixed cortical and white matter lesions.<sup>7</sup> In terms of clinical use in MS, low concentrations of tacrolimus (0.3-0.7 ng/ml) in patients with multiple sclerosis showed minimal toxicity<sup>8</sup> and the use of mycophenolate mofetil or tacrolimus in patients with MS is rarely reported.<sup>9</sup> Cyclosporine monotherapy in MS may have a modest effect in MS that reaches statistical significance but is clinically questionable.<sup>10</sup> In general, the use of combination immunosuppressive therapy, to maximize immunosuppressive effect while reducing the likelihood of drug toxicity, has not been explored in MS clinical trials. We hypothesize that the combination of these drugs (induction followed by low dose maintenance once remission is achieved) may have produced the benefit in our patient and this approach may be worthy of further study. Whether these transplant immunosuppressive agents are comparable in terms of efficacy and adverse events to newer medications used in MS, such as mitoxantrone,<sup>11</sup> remains to be seen.

In general, improvement or resolution of co-existing autoimmune diseases post-transplant are invariably attributed to the effects of long-term immunosuppressive agents, most of which have limited clinical use outside of solid organ transplantation. In our situation, an intriguing but, impossible to prove, possibility remains that the improvement was an effect of the donor organ itself. Despite its high risk, there are some reports of improvement in MS following hematopoietic stem cell transplantation.<sup>12</sup> In the stem cell setting, the immune system is ablated and then reconstituted which is not the case in solid organ transplantation. We note, however, that it is well-recognized in the liver transplant literature that systemic microchimerism of donor cells occurs<sup>13</sup> and donor stem cells have also been reported to persist, and in some cases of close HLA donor-recipient matches, significantly populate the hematopoietic system.<sup>14</sup> We cannot exclude the possibility that systemic microchimerism from a donor without MS may have resulted in some disease modifying effect.

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### Table: Post-transplant Immunosuppression Course

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#### Steroids

**Methylprednisolone** (Solu Medrol, Pharmacia & Upjohn, Mississauga, ON) 500 mg IV/day started intra-operatively with tapering over five days.

**Methylprednisolone** 500 mg IV/day for three days for acute post-transplant rejection on day 11.

**Prednisone** 20 mg orally/day, tapered and stopped on post-transplant day 541.

#### Azathioprine

50 mg orally/day started on post-transplant day 544, increased to 100mg/day on day 662 as leukocyte count stable.

#### Mycophenolate mofetil (Cellcept, Roche-Canada, Mississauga, ON)

2 g orally twice daily until post-transplant day 165, discontinued due to leukopenia. Restarted on post-transplant day 234 and discontinued on day 318 due to leukopenia.

#### Tacrolimus (Prograf, Fujisawa-Canada, Markham, ON)

From post-transplant day 8 due to renal dysfunction. The daily dose was adjusted to achieve a target trough level of 5-10 ng/ml.

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**CONCLUSION**

Post-transplant experience in MS is previously unreported but our experience suggests that in some cases, clinical improvement may occur after transplantation. The post-transplant clinical benefit may be a result of immunosuppressive therapy but the possibility that the donor allograft itself may have had some effect can not be excluded.

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