Equine Antithymocyte Globulin: A Novel Approach for Refractory Immunotherapy Induced Pneumonitis

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BACKGROUND

Immunotherapy-induced pneumonitis (iP) is a rare but potentially fatal immune-related adverse event associated with immune checkpoint inhibitors (ICI). Standard management of iP involves corticosteroids, and in more severe cases the use of immunosuppressants, including mycophenolate mofetil (MMF) or infliximab.[1,2] However, limited guidance and treatments exist for severe cases refractory to these therapies, creating a therapeutic dilemma. This case report presents a unique instance of refractory iP successfully managed with equine antithymocyte globulin (e-ATG), after the failure of corticosteroids and MMF.

AIM

To describe a case of refractory iP treated with e-ATG, highlighting its therapeutic potential in this context.

CLINICAL DETAILS

A 50-year-old female with metastatic melanoma was treated with ipilimumab and nivolumab. Nine weeks into treatment, she presented with shortness of breath, dry cough, and a high-resolution CT scan revealed bilateral ground-glass opacities, consistent with Grade 4 pneumonitis *(figure 1)*.

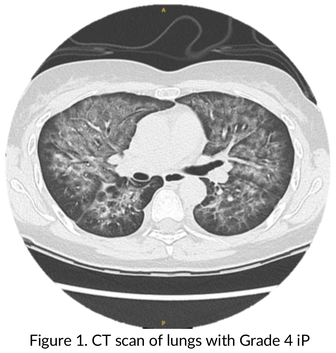

Figure 1. CT scan of lungs with Grade 4 iP
(clinical details and media provided with patient consent)

Despite initial management with an oral corticosteroid (prednisolone 2mg/kg/day for 2 weeks) and escalation to intravenous (IV) therapy (methylprednisolone 200mg/day for 3 days), the patient's respiratory and clinical status continued to decline, necessitating second-line immunosuppression with MMF (titrated up to 1000mg BD).

After two weeks of MMF with no improvement, we explored the use of e-ATG based on its use in immunotherapy induced myocarditis, acute cellular lung transplant rejection and its mechanism of depleting T-lymphocytes, which may play a central role in immunotherapy-related toxicities.[3,4] Initial dosing of 1000mg daily was used, followed by daily dose adjustments in increments of 250mg based on CD2+ and CD3+ counts.

The pharmacist's role in this case included:

- Dose adjusting and monitoring immunosuppression based on CD2+ and CD3+ lymphocyte counts with a target range of 50/µL to 100/µL for each, respectively.
- Ensuring adequate viral, fungal, and bacterial prophylaxis against opportunistic infections. Valganciclovir, posaconazole, and trimethoprim/sulfamethoxazole were used for one, three, and two months post-treatment, respectively.
- Coordinating with a multidisciplinary team to facilitate safe administration of e-ATG, by using appropriate pre-medications, given the high risk of anaphylaxis.

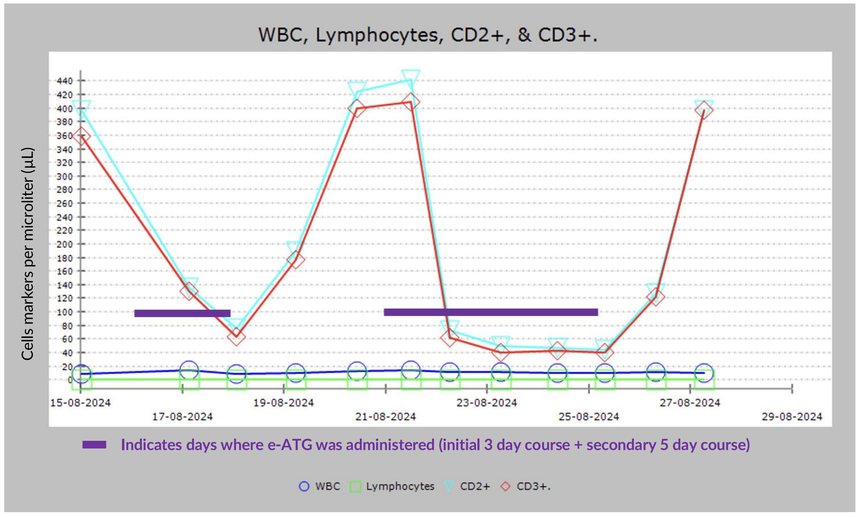

Figure 2. CD2+ and CD3+ lymphocyte count in response to administration of e-ATG

OUTCOMES

CD2+ and CD3+ counts rebounded quickly after the cessation of e-ATG *(figure 2)*, but sustained suppression of C-reactive protein (CRP) occurred during (< 1mg/L) and for days after administration (< 6mg/L) when compared to CRP levels prior to dosing (18mg/L).

Following treatment with e-ATG, the patient's condition began to improve clinically, with marked up trending oxygen saturations *(figure 3)*. They were discharged to home one week after completion of e-ATG and continued weaning prednisolone and supplemental home oxygen.

The patient had no further supplemental oxygen requirement 3 weeks post-discharge. At week 6, a CT chest showed radiological improvement in the lungs, and by week 11, was weaned off prednisolone. After 6 months, a PET/CT scan, showed stable lung changes and no evidence of melanoma recurrence.

DISCUSSION & CONCLUSION

Given the limited published data in this context, the use of e-ATG represents a novel approach for managing refractory iP. Previous cases have utilised IV immunoglobulin, infliximab or cyclophosphamide with variable success,[5] however e-ATG showed rapid and effective immunosuppression, with a unique mechanism by targeting T-lymphocytes directly. This is the first documented case report of the use of e-ATG for severe refractory iP.

e-ATG has potential to be a new therapeutic option, which works rapidly, for severe refractory iP where conventional therapy with high dose IV corticosteroid and MMF have been ineffective. While the initial response was not sustained after the first 3-day course, there was sustained clinical and radiological improvement after the second 5-day course. Suboptimal titration and duration in the first 3-day course may explain the partial but not sustained response.

There were significant pharmacokinetic, pharmacodynamic, and cost considerations associated with the use of e-ATG. Pharmacists played a key role by identifying appropriate doses and durations for treatment, assisting with dose adjustments, CD2/3+ count monitoring, facilitating necessary pre-medications and effective infection prophylaxis. They were also pivotal in ensuring appropriate clinical governance approvals were in place for this high-cost drug, facilitating aseptic preparation and appropriate cold chain management. Their comprehensive approach contributed to the patient's favourable outcome.

Further studies are warranted to confirm efficacy and safety in this setting and to establish the role of CD2+ and CD3+ count monitoring.

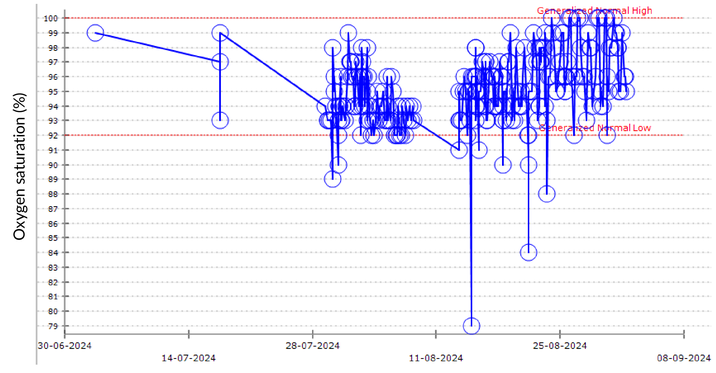

Figure 3. Oxygen saturations of patient during admission (e-ATG given on 16-8-24)

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