22 September 2021

PBAC Secretariat
MDP 952
Department of Health and Ageing
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By email to: pbac@health.gov.au

Re: Re-submission of eculizumab for NMOSD to PBAC meeting November 2021

Introduction

MS Australia is the national voice for people with multiple sclerosis (MS). It is the largest national not-for-profit organisation dedicated to funding MS discoveries and coordinating MS research in Australia and it also works in advocacy and communications, collaborating with stakeholders to benefit thousands of people affected by MS across the country.

MS Australia is writing to support the inclusion of eculizumab on the Pharmaceutical Benefits Scheme (PBS) for people with neuromyelitis optica spectrum disorders (NMOSD). The relatively small NMOSD community in Australia is not represented by a national peak body, and as such, MS Australia is proud to advocate on behalf of those living with NMOSD.

As NMOSD is a rare disease featuring demyelination of nerve fibres (similar to, but different from MS) the medical care often falls under MS specialists. People living with NMOSD also often come to MS Australia and member organisations for assistance and advocacy. One area we are all particularly passionate about is the provision of affordable and accessible treatments that can improve the lives of people with NMOSD.

Our approach in this re-submission

MS Australia made a submission to PBAC in September 2020 to support the listing of eculizumab on the PBS and we commend this previous submission to you (attached).

Having reviewed the Public Summary Document for the initial decision not to recommend eculizumab for listing on the PBS, we have endeavoured to highlight here matters that we feel may require further clarity or emphasis:

1. That NMOSD relapses are generally more severe, last longer and occur more often than MS relapses.

2. That, unlike in MS, **most people** do not recover completely from NMOSD relapses, and are potentially more likely to be left with permanent disability, and at an earlier stage. The benefits of relapse prevention are thus arguably even greater in NMOSD.

3. That there is a great unmet need for relapse prevention in NMOSD, especially compared to MS, for which there are now 14 subsidised therapies to reduce relapses.

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On this basis, and in light of demonstrated efficacy of eculizumab in reducing relapses, we reiterate our support for subsidy of eculizumab for this devastating disease.

NMOSD relapses are more severe, last longer and occur more often than in MS

The presenting symptoms of an acute event or relapse in NMOSD can look similar to an MS relapse and include inflammation of the optic nerve (optic neuritis) causing eye pain, loss of clear vision; inflammation of the spinal cord (acute myelitis) causing pain in spine and limbs, bladder and bowel problems, sensory loss, limb weakness, and numbness; and inflammation in particular areas of the brain (the medulla) causing prolonged hiccups, nausea, vomiting or dizziness[1].

However NMOSD has a distinct pathogenesis from MS: associated with antibodies to aquaporin-4 which are thought to cause damage to astrocytes through complement activation in the CNS[2]. Whilst there are some similarities between NMOSD and MS relapses, there are distinct differences:

- NMOSD is generally more aggressive, with longer and more frequent attacks compared with MS[3,4].
- NMOSD cases are more likely to required acute immunotherapies such as high dose intravenous or oral steroids, plasma exchange and intravenous immunoglobulin. The frequency with which high dose steroids were administered for attacks of NMOSD (58%) was higher than in MS and was similar to previous studies (65–84%)[5,6].

<u>Most</u> people do not recover completely from NMOSD relapses

The effects of an NMOSD relapse can cause long-term disability following an acute event[7]. In a recent study, complete recovery from a relapse was less common in NMOSD (29%) than in MS (56%; $p < 0.001$), similar to that observed previously[6]. ***That is, most people who experience an NMOSD relapse (~70%) will be left with incomplete recovery and potential permanent disability afterwards.***

We argue on this basis, that the impetus for relapse prevention is even more compelling in NMOSD than in MS. Supporting the importance of relapse prevention, the Public Summary document notes from the original hearing that *"The clinician discussed … that many patients do not recover from their first relapse… and emphasised that relapse prevention is the main goal of therapy."*

There is a great unmet need for subsidised, effective treatment in NMOSD

As noted above, NMOSD has a distinct pathogenic mechanism from that of MS[2]. Differential diagnosis of MS from NMOSD is critically important because disease-modifying treatments for MS are inefficacious in or may aggravate NMOSD[8].

In the Public Summary Document and based on results of clinical trials, the PBAC considered that eculizumab was "more effective than best supportive care in reducing relapses".

While the ESC judged that "the magnitude of this effect on disability progression and quality of life outcomes was highly uncertain", it is worthwhile noting that the current treatment guidelines for NMOSD are not based on results of controlled clinical trials, but rather, on case series and uncontrolled comparison studies[9].

Acute relapses are currently treated with steroids and plasma exchange. Treatment to prevent future relapses consists of immunosuppressive therapy or rituximab (and may involve long term use of these treatments). Immunosuppression is achieved with steroids, azathioprine, mycophenolate, methotrexate or less commonly with cyclophosphamide. Rituximab is currently favoured to be the most effective therapy for the prevention of relapses in NMOSD[10, 11] and is not subsidised on the PBS, but currently funded through hospital pharmacy budgets in Australia. **However, it is estimated that**

25% of patients with NMOSD will continue to have relapses on rituximab. There is therefore a clear need for additional treatment options for NMOSD.

We note that in Australia for MS, there are currently 14 treatments subsidised by the PBS for relapsing disease, including infused monoclonal antibody therapies (as are rituximab and eculizumab). Access to a range of subsidised treatments is essential because many people who fail to respond to one specific therapy often respond well to other available therapies. Although a rarer disease than MS, we support equitable access to a range of subsidised relapse treatments for NMOSD patients.

The personal impact of NMOSD on the quality of life of the person diagnosed and their family and friends can be devastating. This is exemplified in excerpts here from our original submission, with the burden illustrated in further case studies below:

> *"My marriage broke up because of NMO, the strain that it put on our relationship was enormous…. That cost to me was enormous."*
>
> *"The children witnessing me having these massive spasm attacks, being in bed, not being able to speak or move. It's traumatic for them. I know my daughter, especially, being a little bit younger, was traumatized."*
>
> *"Initially, it was horrendous. You can't see, you can't walk. It affects relationships. I don't go to work and I don't have that feeling of being capable…"*
>
> *"I haven't been able to work. I can't work because I don't have the stamina anymore. Even one phone conversation will exhaust me."*
>
> *"Well, my peripheral vision has gone in both eyes. I'm legally blind in the right eye. I can't drive. Just doing standard chores around the house, like washing up, or just cooking things. I've got to sit down."*

There is a great unmet need for subsidised effective therapies to prevent NMOSD relapses and their devastating consequences.

Our understanding of eculizumab (Soliris) as an effective treatment option for NMOSD

Eculizumab has been demonstrated to dramatically reduce the risk of relapse in a randomised, placebo-controlled clinical trial[12]. This treatment effect is of particular importance, as studies show that the **accrual of disability in NMOSD almost exclusively occurs as a result of relapses** with a secondary progressive disease course being rare, unlike MS[3].

There were four clinical trials sponsored by Alexion Pharmaceuticals on the use of eculizumab in an NMOSD patient population. Results of these clinical trials report that eculizumab reduces relapses, and can maintain or reduce the level of disability in patients with NMOSD[5,12]. It is generally well tolerated and has been approved for the treatment of NMOSD by the FDA and the European Medicines Agency[6].

Conclusion

We support affordable access to all proven treatment options to increase the opportunity for people with NMOSD and their doctors to access effective therapy. We would strongly support PBS listing for eculizumab for patients with NMOSD who have relapsed on existing therapy. Reducing disease relapses will improve quality for people with NMOSD and their loved ones, enabling their full participation in social and family life, and employment and reducing the significant mental health burden associated with the fear of relapses, disability progression and an unknowable future.

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Case study 1

1. **What is your age and family circumstances?**

Female, aged 45, married with 15 year old son, and is in receipt of an NDIS package (which indicates a level of disability/functional impairment necessary to meet NDIS access requirements).

2. **How long since you were diagnosed?**

Four years ago when aged 41.

3. **Were you diagnosed with your first relapse of NMOSD, or did it take longer?**

Had small neurological episodes for approximately one year before the first major attack, which manifested through severe vomiting and numbness throughout body. Resulted in an initial three-month long hospital stay.

4. **Did you receive another diagnosis before NMOSD?**

Examination and lumbar puncture following first attack led to NMOSD diagnosis, neurologist already suspected NMOSD.

5. **What are the major symptoms you experienced with your relapses? Do those symptoms remain with you now?**

Symptoms include: nerve pain, dull burning sensation, uncontrollable vomiting, numbness in fingers and legs that spreads to other parts, chest band tingling, (tightness and tingling similar to "MS hug"). Also lost continence and balance at this time. Initial steroid treatment helped but nerve pain persists, stretching and other exercise helps a little. Also susceptible to hot weather, causes severe fatigue.

6. **Has having NMO had an impact on your quality of life? What are your major challenges?**

Yes, big impact on quality of life for person diagnosed, family and friends. Physical and mental challenges persist. Greatest impact is fear of a relapse and fear of getting worse, underlying fear of the unknown and what the future holds.

This person's major form of exercise pre-diagnosis was running, but she is unable to run anymore due to severe nerve pain. Also can't bear unexpected touch such as a pat on the back.

Significantly reduced social life and loss of confidence in social and family interactions. This has also impacted on the family – whole family is less active, doesn't socialise much.

7. **How do you currently manage your NMO symptoms? Do you feel like you have good control over the symptoms/effective management?**

Exercise helps a lot. Able to access Dept Veteran's Affairs free mental health services. Was unable to walk for 22 months after first attack. Completed a two-year "Open arms" (veterans and families counselling service) course to assist with mental health.

8. **When you are using a treatment (for NMOSD relapse/for NMOSD symptoms), what needs to improve for you to feel as though the treatment has worked?**

Currently access a range of medications – oral steroids, Lyrica (for nerve pain), antidepressant (to assist with sleep), 6-monthly rituximab infusions. All of these treatments need to be effective to manage symptoms, stop inflammation, stop new lesions forming,

9. **If a treatment improved those things, what would that mean to you in your everyday life, that is, what would you be able to do that you couldn't do now?**

Would give my family and I the confidence to get out and about and have a normal family life. Improved treatment would help the family relax. The family can tend to be overprotective and limit activities, as they have witnessed what an attack is like and also understand the impact of the ongoing symptoms.

10. **If you were having a new treatment, what kind of information or support would you need to feel comfortable with the new treatment? Would it matter how the medication was delivered? (e.g. by tablet or by infusion?)**

Interested to understand the clinical trial information and exactly what patients in the trials experienced. Drugs like rituximab don't work for everyone, so assume it would be the same for any new drug. NMOSD affects everyone differently (similar to MS) so eventually need multiple treatment options. Oral is obviously the better option but don't really care as long as it works!

11. **In relation to NMO, what would you most like to see from new treatments? This might be about the way they are administered, the effects they have on NMOSD, the side effects they have, cost or things like that.**

Want to have some choice in treatments tailored to individual disease course, available on the PBS to make them affordable, need to prevent relapses and take away the "fear factor" of disease progression. The fear of relapse and having no options, especially if a drug like rituximab doesn't work, for the patient and her family, is significant.

12. **If you had to tell someone who knows nothing about NMOSD about the effects that NMOSD has had on your life and the lives of those you love, what would you say?**

It forces you to live only day to day and not plan anything much for the future, it can cause marriage separation, family and friends relationship breakdowns, loss of employment.

Limited social activity has been made much worse during the pandemic.

Case study 2

1. **What is your age and family circumstances?**

Female, aged 58, divorced from first husband following diagnosis, has two adult children, has since re-partnered.

2. **How long since you were diagnosed?**

9 years ago, had first major episode in 2012.

3. **Were you diagnosed with your first relapse of NMOSD, or did it take longer?**

Longer, took another year for the next relapse to occur.

4. **Did you receive another diagnosis before NMOSD?**

Initially diagnosed with transverse myelitis, needed an "optical coherence tomography" test to determine a diagnosis of NMOSD. Other events and symptoms had been occurring earlier (over a 20 year period) such as loss of feeling. This was put down to brachial plexus neuritis and/or suspected MS, but in retrospect realise this was early symptoms of NMOSD.

5. **What are the major symptoms you experienced with your relapses? Do those symptoms remain with you now?**

With the initial attack in 2012, this patient experienced blurred vision, uncontrollable eye movement, weak limbs, muscle spasms, burning sensation, bladded incontinence, cognitive issues especially with memory loss, pins and needles, legs kept collapsing, couldn't walk far. These symptoms lasted for around two weeks.

A second attack in 2013 affected her diaphragm which ended her music teaching career as she could no longer sing; her voice was reduced to a whisper and she had to undertake speech therapy to make some recovery.

6. **Has having NMO had an impact on your quality of life? What are your major challenges?**

This person has had to reinvent herself. Her marriage failed and she had to give up activities such as volunteering with the local fire brigade, as well as her teaching career. This was very traumatic and isolating.

7. **How do you currently manage your NMO symptoms? Do you feel like you have good control over the symptoms/effective management?**

Takes a range of medications e.g. azathioprine, though this stopped working after two years and resulted in severe side effects. Currently takes mycophenolate which she believes is beneficial in preventing major flare ups, though still experiences minor flare ups.

8. **When you are using a treatment (for NMOSD relapse/for NMOSD symptoms), what needs to improve for you to feel as though the treatment has worked?**

Flare ups need to be prevented. This will give her confidence that the disease is being managed. Fear of future flare ups is significant and debilitating. Symptoms need to be managed to the extent that the patient can enjoy some quality of life.

9. **If a treatment improved those things, what would that mean to you in your everyday life, that is, what would you be able to do that you couldn't do now?**

Plan for more family and social activities, and other interests such as interstate travel. Regain confidence and a more positive outlook on life without the fear of relapse. Hard to think about this as you adjust your life to suit your circumstances and disease journey over a long period of time. Hard to imagine anything different.

10. **If you were having a new treatment, what kind of information or support would you need to feel comfortable with the new treatment? Would it matter how the medication was delivered? (e.g. by tablet or by infusion?)**

No real preference as long as the medication works. Tablets have the advantage of being portable, preferred if you are travelling for example.

11. **In relation to NMO, what would you most like to see from new treatments? This might be about the way they are administered, the effects they have on NMOSD, the side effects they have, cost or things like that.**

Need to understand any long-term side effects, need as much information on all aspects of any new treatment to make an informed choice.

12. **If you had to tell someone who knows nothing about NMOSD about the effects that NMOSD has had on your life and the lives of those you love, what would you say?**

Impact on life in one word – devastating! It causes depression, mental health issues and lack of hope. Devastating for teenage children to witness a parent's NMPOSD attack. Family members don't want to discuss the disease. This causes the person diagnosed to switch into "survival mode" - "you can't get those years back!". Had to give up career in teaching and life with the fear that medications would stop working. Was traumatised when told by a health professional that 50% of people with NMOSD die young.