Canadian Headache Society
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Scientific argument: combination of onabotulinum toxin type A and a CGRP monoclonal antibody is warranted to treat refractory migraine

To whom it may concern,

It has come to the attention of the members of the Canadian Headache Society that many insurance companies are now refusing to cover the combination of Botox and a CGRP monoclonal antibody (BTX + CGRP MAB). Currently available CGRP monoclonal antibodies are erenumab (Aimovig), galcanezumab (Emgality), Fremanezumab (Ajovy) and eptinezumab (Vyepti).

There is no medical reason to deprive patients of this therapeutic combination. We have heard multiple clinicians voicing concerns for their patient's health as they are forced to choose between two drugs that had both significantly contributed to an improvement in their quality of life.

Combining medications with different mechanisms to optimize the treatment of a disease is very common in medicine. Epilepsy, hypertension, diabetes and cancer are all treated with multiple combinations of drugs, some of them quite expensive (1-3). Chronic migraine is an underdiagnosed and undertreated condition that may lead to significant disability and require polytherapy.

There is no medical risk (theoretical or observed in the clinic) to combine Botox and CGRP MABs. Many currently used oral migraine preventives have significant side effects and long term toxicities that are more harmful to patients than Botox and probably CGRP MABs (4).

There are scientific arguments supporting the BTX + CGRP MAB combination. Indeed, Botox does inhibit the release of CGRP, but other mechanisms could make them complementary:

1. Botox inhibits the release of CGRP from C fibers
2. Antibodies (data available on fremanezumab) block CGRP mostly on A-delta fibers (5)
3. Botox also inhibits the release of other peptides and activity of channels playing a role in neurogenic inflammation (6, 7)
4. Botox is injected locally, CGRP monoclonal antibodies act more diffusely

There is a strong clinical impression from many experts around the world that some patients with chronic migraine who get a partial benefit from Botox are further improved by the addition of a CGRP monoclonal antibody. In the PREEMPT trials, patients improved on a mean of 8 days per month from a baseline of 20 days (8). That means that a patient with a baseline of 22 days per month treated with Botox with a 50% response (reaching a frequency of 11 days per month) would still qualify for a CGRP MAB (8 days per month). Also, the clinically meaningful response in chronic migraine is usually considered to be 30%, since these patients may be severely disabled (9, 10).

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The headache frequency is not the only outcome to take into account when treating chronic migraine (11). Headache intensity, interictal symptoms such as fatigue and neck pain, co-morbid mood disorders, neck pain, effectiveness of acute treatments and resistance to the trigger load are all important aspect of the patient's quality of life.

The financial argument to deprive patients of access to care is not sufficient. A combination of a CGRP antibody with Botox would cost approximately 10 600 CAD per year (12 X 600 + 4 x 850). Other medications in neurology are more costly and not necessarily more cost-effective than a MAB/Botox combination. For example, the cost of natalizumab for multiple sclerosis is $40 000 per year (12). We are concerned that the stigma on migraine may lead to a different perception of this disease despite clear data on costs and burden (13-16). The global costs associated with migraine are 15 000 per year for low frequency and 25 000 CAD for high frequency and chronic migraine(17).

The evidence for the effectiveness of the BTX + CGRP MAB combination has been duplicated by many experienced teams across the world with different methodologies (18-28). The current clinical thinking is therefore that this combination should be offered to patients who are not sufficiently improved by only one of these therapies. The goal for migraine control is the lowest frequency and intensity achievable.

In summary, although the Canadian Headache Society recognizes the financial arguments leading to the decision of declining the BTX + CGRP MAB combination, we feel that this combination is medically warranted and cost-effective for some refractory patients, usually managed by neurologists and headache specialists.

We invite insurance companies, employers, and any other interested stakeholders to contact us to discuss this important clinical situation. The Canadian Headache Society is committed to the improvement of patient care and research in the headache field.

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