TITLE: Glatiramer Acetate for the Treatment of Clinically Isolated Syndrome: A Review of the Clinical Efficacy and Guidelines

DATE: 24 September 2012

CONTEXT AND POLICY ISSUES

Clinically isolated syndrome (CIS) is a single episode of demyelination in the central nervous system that lasts longer than 24 hours. Patients with CIS may advance to multiple sclerosis (MS). Previous studies have indicated that 10 to 20 years after the initial diagnosis of CIS, the risk of progressing to clinically definite multiple sclerosis (CDMS, defined as the appearance of new or recurrent neurological abnormalities lasting at least 48 hours and preceded by a fairly stable or improving neurological state for at least 30 days in the PreCISe study) was 55% to 80% for patients with magnetic resonance imaging (MRI)-detected brain or spinal cord lesions, and about 20% for those with negative MRI findings.

Early treatment of CIS may be beneficial if it is initiated after the first clinical attack, instead of waiting until a second attack occurs. Previous studies have suggested that interferon ß-1a, interferon ß-1b and glatiramer acetate (GA) delay the onset of CDMS in patients with a first appearance of a neurologic event. GA is a synthetic analogue of myelin basic protein – an antigen which is related to the pathogenesis of MS. Its mechanism of action is associated with producing anti-inflammatory effect, immunomodulatory effect, and neuroprotective or neuroregenerative effects. Health Canada approved the subcutaneous use of GA as an immunomodulator in 1997.

A double-blind, placebo-controlled RCT (PreCISe) published in 2009 suggested that GA was superior to placebo in prolonging the time to conversion to CDMS but its effect on disability was unclear. More patients in the GA group discontinued the treatment due to adverse events compared with placebo, and injection-site reaction was the most frequently reported adverse event. Given the uncertain clinical benefit from the PreCISe study and undetermined cost-effectiveness regarding the use of GA for CIS, the Canadian Expert Drug Advisory Committee recommended that it not be listed for this indication.

The purpose of this report is to review new evidence regarding the efficacy of GA for the treatment of CIS since the publication of the PreCISe study. The evidence-based clinical practice guidelines for the treatment of CIS are also reviewed.

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Research Questions

1. What is the clinical evidence regarding the efficacy of glatiramer acetate for the treatment of clinically isolated syndrome?

2. What are the evidence-based guidelines for the treatment of clinically isolated syndrome?

Key Message

No new evidence regarding the efficacy of glatiramer acetate for the treatment of clinically isolated syndrome was identified after 2009. No evidence-based guidelines for the treatment of clinically isolated syndrome were identified.

Methods:

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1980-) via Ovid, the Cochrane Library (2012, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and August 23, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, and evaluated the full-text publications for the final article selection, according to the selection criteria present in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult patients with clinically isolated syndrome</th>
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<tbody>
<tr>
<td>Intervention</td>
<td>Glatiramer acetate</td>
</tr>
<tr>
<td>Comparator</td>
<td>Interferon β-1a</td>
</tr>
<tr>
<td></td>
<td>Interferon β-1b</td>
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<td></td>
<td>Placebo</td>
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<tr>
<td>Outcomes</td>
<td>Patients progressing to CDMS</td>
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<td></td>
<td>Time to progression to CDMS</td>
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<td></td>
<td>Mortality</td>
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<td></td>
<td>Hospitalizations</td>
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<td>Quality of life</td>
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<td>Time to disability</td>
</tr>
<tr>
<td>Study Designs</td>
<td>Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and clinical practice guidelines</td>
</tr>
</tbody>
</table>

CDMS = clinically definite multiple sclerosis
Exclusion Criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications, were abstracts or conference proceedings, were included in a selected systematic review, or were published prior to 2009.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 314 citations. Upon screening titles and abstracts, 310 citations were excluded, and four potentially relevant articles were retrieved for full-text review. Of the four potentially relevant reports, none of them met the inclusion criteria. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Additional references of potential interest are provided in Appendix 2.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

The research questions regarding the efficacy of glatiramer acetate for patients with clinically isolated syndrome cannot be answered, as no new RCTs published since the PreCISE study were found.

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REFERENCES


APPENDIX 1: Selection of Included Studies

314 citations identified from electronic literature search and screened

310 citations excluded

4 potentially relevant articles retrieved for scrutiny (full text, if available)

0 potentially relevant reports retrieved from other sources (grey literature, hand search)

4 potentially relevant reports

4 reports excluded:
- irrelevant population (1)
- irrelevant intervention (1)
- systematic reviews but included the PreCISE study only (2)

0 reports included in review
APPENDIX 2: Additional References of Potential Interest