TITLE: Increased Dose or Decreased Dosing Interval of Biologics: Clinical Effectiveness

DATE: 28 July 2010

RESEARCH QUESTION:
What is the clinical effectiveness of an increased dose or a decreased dosing interval of biologics for the treatment of conditions other than rheumatoid arthritis?

METHODS:
A limited literature search was conducted on key health technology assessment resources, including PubMed, OVID EMBASE, the Cochrane Library (Issue 7 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and July 14, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

RESULTS:
HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials.

Nine relevant randomized controlled trials were identified pertaining to the clinical effectiveness of an increased dose or a decreased dosing interval of biologics for the treatment of conditions other than rheumatoid arthritis. No relevant health technology assessment reports, systematic reviews, or meta-analyses were identified. Additional information that may be of interest has been included in the appendix.
OVERALL SUMMARY OF FINDINGS:

Overall, evidence for the clinical effectiveness of an increased dose or a decreased dosing interval of biologics for the treatment of conditions other than rheumatoid arthritis is varied. For patients with Crohn’s disease:

- shorter dosing interval of certolizumab\(^2\) was no more effective than conventional dosing in terms of treatment response and remission
- two studies found fewer Crohn’s-related surgeries and hospitalizations for patients taking adalimumab with shorter dosing intervals\(^3,4\) and one study did not find a difference in response rates.\(^5\)

In patients with psoriasis:

- higher doses of adalimumab\(^6\) and shorter dosing interval for entercept\(^7\) were associated with higher response rates
- higher doses of golimumab were more effective for those with more severe disease (3% surface area or more) than for those with more mild cases.\(^8\)

For patients with psoriatic arthritis:

- shorter dosing interval with entercept resulted in similar efficacy to the conventional schedule\(^7\)
- increased doses of golimumab resulted in slightly better American College of Rheumatology 20% improvement criteria in patients with psoriatic arthritis.\(^8\)

For patients with akylosing spondylitis\(^1\) and psoriatic arthritis taking Infliximab,\(^9\) no conclusions regarding dosing increases were presented in the included abstracts but could potentially be reported in the full text articles. No relevant information pertaining to the treatment of ulcerative colitis was identified. Further details of the included studies can be found in Table 1.

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Study type</th>
<th>Biologic Drug, Dosing</th>
<th>Results and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s disease</td>
<td>RCT</td>
<td>Certolizumab 400 mg every 2 or 4 weeks after induction dosing.</td>
<td>In patients with secondary failure to infliximab, maintenance doses of 400 mg certolizumab delivered at 2 week or 4 week intervals had similar efficacy.(^2)</td>
</tr>
<tr>
<td>RCT</td>
<td>Adalimumab 40 mg every other week, or 40 mg every week after induction dosing.</td>
<td>Continuous treatment with 40 mg adalimumab weekly or every other week had similar efficacy and both were more effective than induction therapy followed by placebo.(^3)</td>
<td></td>
</tr>
<tr>
<td>RCT</td>
<td>Adalimumab 40 mg every other week or 40 mg every</td>
<td>Weekly treatment with 40 mg adalimumab has associated with higher relative reductions in 12 month all-cause hospitalizations and 12 month risk of Crohn’s related hospitalizations than 40 mg every other week.(^4)</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1: Details of included studies

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Study type</th>
<th>Biologic Drug, Dosing</th>
<th>Results and Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akylosing spondylitis</td>
<td>RCT</td>
<td>Adalimumab 40 mg every other week or 40 mg every week after induction dosing.</td>
<td>No significant differences observed between treatment outcomes in patients receiving 40 mg adalimubab weekly or every other week.&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>RCT</td>
<td>Adalimumab 40 mg every other week or 80 mg every other week after induction dosing.</td>
<td>Patients receiving adalimumab 80 mg every other week had higher response rates (as per the Psoriasis Area and Severity Index) than those receiving 40 mg every other week.&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Psoriasis and psoriatic arthritis</td>
<td>RCT</td>
<td>Entercept 50 mg twice weekly or 50 my weekly.</td>
<td>For patients with psoriasis, 50 mg entercept twice weekly was more effective than 50 mg once weekly. For patients with psoriatic arthritis, response rate was similar between 50 mg weekly and 50 mg twice per week.&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>RCT</td>
<td>Golimumab 50 mg every 4 weeks or 100 mg every 4 weeks.</td>
<td>Response rate after 14 weeks in patients with psoriatic arthritis was slightly higher for those taking 50 mg golimumab every 4 weeks than 100 mg every 4 weeks. For patients with at least 3% body surface area with psoriasis, response rates were higher in the 100 mg group than in the 50 mg group.&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>RCT</td>
<td>Infliximab 5 mg/kg every 8 weeks or 10 mg/kg after</td>
<td>Patients receiving 5 mg/kg infliximab could escalate dose to 10 mg/kg if response was lost. No specific conclusions regarding dose escalation presented in the abstract but infliximab was found to have high clinical</td>
</tr>
<tr>
<td>Patient Group</td>
<td>Study type</td>
<td>Biologic Drug, Dosing</td>
<td>Results and Conclusions</td>
</tr>
<tr>
<td>---------------</td>
<td>------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>induction dosing or lost response.</td>
<td>efficacy.</td>
</tr>
</tbody>
</table>

mg = milligram; mg/kg = milligram per kilogram; RCT = randomized controlled trial
REFERENCES SUMMARIZED:

Health technology assessments
No literature identified.

Systematic reviews and meta-analyses
No literature identified.

Randomized controlled trials

Akylosing spondylitis


Crohn’s disease


Psoriasis and Psoriatic arthritis


randomised double blind multicentre trial. BMJ [Internet]. 2010 [cited 2010 Jul 14]; 340:c147. Available from: 
http://www.bmj.com/cgi/content/full/340/feb02_2/c147?view=long&pmid=20124563
PubMed: PM20124563


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856065 PubMed: PM17114188

PREPARED BY:
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439
APPENDIX – FURTHER INFORMATION:

Health technology assessments

10. Assai N. Overview of anti-TNF-á drugs for refractory inflammatory bowel disease [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009 (Technology overview number 52) [cited 2010 Jul 14]. Available from: http://www.cadth.ca/media/pdf/O0479_Anti_TNF_a_Drugs_for_Refractory_Inflammatory_Bowel_Disease_to_e.pdf

Systematic reviews and meta-analyses

Note: Reprinted with edits in 2009, no change to search dates or to conclusions

Economic information


Non-randomized studies


Review articles


Additional references
