Reviewer's report

Title: Cost-effectiveness of adding rituximab to the existing treatments of splenectomy and thrombopoietin receptor agonists (TPO-RA) for steroid-resistant idiopathic thrombocytopenic purpura (ITP)

Version: 2
Date: 18 August 2014
Reviewer: Anneke Brand

Reviewer's report:

Guideline questions:
1. Is the research Q well-defined: yes
2. Are methods appropriate and well defined: being no HTA expert, I can only judge clinical assumptions of the model, these seem sound
3. Are the data sound: yes
4. Are relevant standards for reporting applied: yes
5. Are discussion and conclusion balanced and supported by the data: yes (see minor remarks below)
6. The (many) limitations are clearly stated
7. Yes, the authors acknowledge on published work
8. Title and abstract reflect study outcome
9. The writing is clear

Comments to authors

General
The authors evaluated cost-effectiveness of two scenario’s of implementing rituximab (RI) as third line treatment of ITP within Japanese guidelines (which recommend 1 corticosteroids 2 splenectomy (SP) and 3 several third line options including RI and TPO-RA’s). The endpoint was a platelet ct > 30 x 10E9/L. The period chosen 2 years (which is a limitation considering a chronic disease). Although the choice of >30 instead of > 50 is indeed more realistic with respect to withholding treatment and bleeding complications from ITP, it should be noted that in case of interventions (delivery, surgery) not related to ITP, platelet cts of > 50 are often required (unforeseen costs). The authors conclude that adding RI either after failure of SP-TPO-RA or after failure of SP is both less costly compared to current SP-TPO-RA treatment. Although cost-savings are larger with option SP-RI-TPO-RA they do not want to underscore this, because in their model this option is associated with more mortality and morbidity.

Although well-written and weaknesses are extensively discussed, analysis of this type are however based on assumptions. Variations in treatment responses are in the opinion of the authors more important than variations in the costs of drugs.
They do not consider cost effects of variations in the occurrence of AE and emergency treatment. This weaknesses may be underscored in the discussion. However, although many assumptions can be questioned, the true incidence is difficult to estimate and poses a challenge for prospective cost-effectiveness studies.

Mortality/morbidity from SP (despite platelet cts > 30), as shown in table 1 add to total 2 year costs of variants 1,2 and 3. If the authors include the variant of SP only this would make it easier to follow the costs in options 1-3.

Discretionary revisions:

Background
Q1 Page 5, line 89/90: 2 courses RI may be sufficient for a proportion of patients, however (line 93) although 60% of patients show a sufficient platelet increment, the median response duration is limited and after 5 years 20-25% have sufficient platelet cts. (ref 7)

Q2 Page 5, line 94: referral to Harrison: highly evidenced does not include dose or number of treatments of RI.

Treatment option
Q3 Page 7, line 133: TOP-RA=TPO-RA
Q4 Page 8, line 140: before SP (and before RI if RI is applied before SP) vaccinations must be administered.

Q5 Page 10, line 182: 4 weeks of treatment for PE is unclear, anticoagulant treatment is 3 – 6 months and has its own complications and need regular blood control.

Model design
Q6 Page 10, line 188: always return to corticosteroids after failure of SP/RI/TPO-RA is not correct. Generally from the wide list of third line options (page 5, lines 81), drugs are tried. Also the assumption that in case of option 1,2,or 3 failure the platelet ct will be < 30 is not black and white, but acceptable in this model. Another minor weakness?

Discussion
Q7 Page 15, line 276: sates? I cannot find this in a dictionary.
Q8 Page 17, line 318: can be instead of are completely cured with rituximab.

Minor essential remarks:

Background
Q9 Page 4, line 62: it should be noted that although mortality in patients with platelet cts < 30 while on third line treatment is 4.2 fold higher than in healthy individuals (ref 2), in this reference 50% was the result of immunosuppressive treatment and not because of thrombocytopenia (bleeding). Moreover these data were obtained prior to availability of RI and TPO-RA, using third line drugs not
Methods

Q10 Page 7, line 120: Give a motivation why the cost-effectiveness analysis was set at 2 years and not at for instance 1 and 5 years? Although in the discussion it is mentioned that TPO-RA is licensed in Japan since 2011, most other input is from North-West European origin.

Treatment option

Q11 Page 9, line 153-155: the life-long risk of sepsis after SP is estimated up to 10% and up to 5% of patients on TPO-RA suffer a thrombotic event and 15% need control because of liver function test disturbances. Activation of HBV can be expected with RI. How these percentages are used in the 2 year observation period should be clarified.

Model design

Q12 Page 10, lines 172-188. See also remark for page 9 above. The estimated incidence of the distinct AEs in the various treatment arms during the 2 year study period (that determine costs of arms 1-3) cannot be found in text or table 1.

Model inputs

Q13 Page 11, line 209: physicians honoraria and out of hospital costs (missing working days of the patient, home care) are not included, please mention this explicitly.

Discussion

Q14 Page 17, line 320: I cannot find the reference of Boland [9]

Q15 Page 18, line 324-9: difference in option 2 and 3 are largely due to AE and emergencies, which are based on the "weaker" assumptions in the model. Can more clearly be explained why emergency incidences/treatment costs are estimated higher in option 3 as compared to option 2.

Q16 Table 1: mention in the legends what is indicated between [], apparently these are the references

Q17 Table 2: give for sepsis, PE and IVIG in table legend that these are the costs of the event, (not corrected for the number of events expected in 28 days).

Q18 Table 3: how is the period of platelet cts > 30 calculated? Or mention this in method section and refer.

Q19 Fig 1 Splenectomy is included as cost factor in all three scenario’s, why not show the costs of SP alone (not needing third line treatment, but leading to death and costs from AEs; this would enhance the message for non-Japanese countries who tend to replace SP as second line treatment for RI and TPO-RA prior to SP.

Q20 Fig 2 is not very helpful and can be better explained in text.
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Misconduct
I did not find signs of misconduct, duplication or falsification. The issue of sponsoring is addressed in the associated letter by Dr Kikuchi.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I have no competing interest in relation to this paper. I have no financial relationships to disclose.