Response to NICE Appraisal consultation document for the use of Romiplostim for the treatment of chronic immune or idiopathic thrombocytopenic purpura

On behalf of the UK ITP association and as a Haematologist I would like to formally express my disappointment with the preliminary recommendations for the use of Romiplostim for chronic ITP in England and Wales as summarised in the recent appraisal consultation document. There has been a large response to this document from the ITP association and Haematology community (who organise the overall care the many facets of the care for patients with the complicated disease of immune thrombocytopenia (ITP) in the UK) The overwhelming (100%) response has been disappointment and concern.

I would like to put forward before the committee a number of points and arguments which I would wish to be taken into consideration during this period of consultation.

- Immune thrombocytopenia (ITP) is an extremely variable disease – although some patients have no symptoms or minimal bruising others experience serious bleeding which may be life threatening. The severity of thrombocytopenia correlates to some extent but not completely with the bleeding risk and therefore treatment is individualised to manage the patient symptomatically rather than aimed at achieving a specific platelet count. Response to the various treatments available are variable with small numbers of patients either failing to respond, i.e. they are refractory, or having very short-lived responses to the currently available treatments. It is this small group of patients where new therapies are needed. An unofficial estimate of the numbers of patients falling into such a category is likely to be in the order of approximately 2:5000 population. ***The advent of a new group of effective agents with a different mode of action is therefore an important addition to the treatment portfolio for this complex but small number of patients with refractory or rapidly relapsing symptomatic ITP***

- None of the currently available treatments if used long term (even with intermittent use) are risk free with many patients being unsuitable for such treatments and developing morbidity (e.g. recurrent infections, viral reactivation , osteoporosis) or even mortality (e.g. from infections Portielje et al Blood 2001:97;2549). ***The advent of a new group of effective agents with a different mode of action which is not immunesuppressive is therefore an important addition to the treatment portfolio for patients with relapsing symptomatic ITP***

- Regarding clinical interpretation of the evidence much emphasis seems to be placed on the fact that there are no clinical trial data to demonstrate the relative effectiveness of Romiplostim compared with other active treatments. Given the immense variability and rarity of severely affected patients with cITP such data is likely to be impossible to acquire. In addition clinically it is not only the immediate efficacy of a treatment that needs to be considered but the duration of effect, the potential side effects of the treatment and the availability of other treatments.

- Since the committee started this appraisal anti-D has been withdrawn from the European market, the use of IvIg (which is a blood product carrying the fear of transmission of infectious disease) has been restricted due to short supplies and potentially serious lethal effects of Rituximab in ITP have been published (*Carson et al Blood 2009;113:4834-40*)

In response to the specific questions:

i) Do you consider that all of the relevant evidence has been taken into account?

No - not enough attention has been paid to the complications of currently used treatments for ITP (e.g secondary malignancy after alkylating agents *Krause* Med Pediatr Oncol 1982:10(1):61-5; sterility after alkylating agents; renal effects of cyclosporin *Kappers-Klunne BrJHaematol2001;11491*):121-125; Progressive multifocal leucoencephalopathy following rituximab, *Carson et al Blood 2009;113:4834-40*)

In addition:

- since the committee reviewed the evidence an International consensus report for the management of primary ITP has been published (Provan et al Blood http://bloodjournal.hematologylibrary.org/misc/rights.dtl#repub_requests This supports the use of TPO agonists in the management of symptomatic refractory ITP.

- as outlined above the availability of data from RCTs comparing Romiplostim to currently available treatments is unlikely to ever be achievable given the extremely variable nature of both this autoimmune disease, the severity of the clinical condition and the response to treatment. In addition apart from IvIg and steroids no other drugs are licensed for the use in ITP. The two RCTs against placebo demonstrate unequivocally the efficacy of Romiplostim producing a sustained response both in terms of the platelet count and symptoms.

ii) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?

The cost effectiveness calculations appear to have been carried out solely for patients receiving long term Romiplostim and achieving a target platelet count of 30 and 50 x 10^9/l. The numbers of patients for whom Romiplostim will be considered is likely to be less than that outlined in the appraisal and I note that this is acknowledged in 4.12. In assessing a response rather than achieving a specific platelet response clinicians are more likely to look for symptom control and some of the use will be short term for elective procedures, such as preoperatively where a predictable and sustained response is required (not possible with current therapies). In addition as ITP is such a variable condition clinicians are likely/should be encouraged to consider withdrawal of therapy to see if continuation is indeed necessary symptomatically. These measures are likely to result in reduced the use of Romiplostim both overall and for the individual patient.

I would also like to comment that classical cost effectiveness models may not be appropriate for the situation where no other treatments are effective e.g. patients who have refractory non responsive ITP.

I will not comment on the vial wastage which I can appreciate may be an issue in calculating the cost effectiveness.

iii) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

No for the reasons given above and the inclusion of the TPO agonists in the recent international consensus report: Proven et al 2009
http://bloodjournal.hematologylibrary.org/misc/rights.dtl#repub_requests

iv) Are there any equality related issues that need special consideration that are not covered in the ACD?

Yes - has been approved for use in Scotland

In summary therefore I hope the committee will review the situation and accept that

- Romiplostim is an advance in the treatment of ITP which can be used effectively for the small group of severely symptomatically affected patients who are refractory to or have significant complications form the currently available treatments for whom treatment options are extremely limited. It is for this group that the addition of Romiplostim to the portfolio of treatments for ITP is indicated.

- To design and conduct RCTs of Romiplostim against other treatments is unlikely to be feasible but that the effectiveness of this agent for refractory ITP has been shown in the two available RCTs

- The trials using suggest good tolerability and apparent low toxicity of Romiplostim in comparison to many of the other treatments in use for cITP

and approve the use of Romiplostim in a defined selected group of patients with cITP

[redacted]
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