NICE Single Technology Appraisal of Rituximab. Response to the ACD on behalf of Vasculitis UK.

Summary (see also supplementary notes)

Vasculitis UK is the only national registered charity representing the interest of patients suffering from all types of systemic vasculitis in the UK. The decision to refuse the application from Roche has shocked the vasculitis community and caused great dismay.

- We consider that the initial decision of the Appraisal Committee **not** to support the use of rituximab for treatment of AAV is seriously flawed . We accept that there was certain important evidence that was not available for the committee's consideration previously that is now available.
- We consider that some of the evidence previously submitted to the Committee was unintentionally misleading.
- We consider that the Committee failed to appreciate the seriousness of the impact of the withdrawal of this important new drug on the wellbeing and possibly the survival of people with AAV.
- AAV is a relapsing disease. **All** patients with AAV are potentially subject to relapse.
- There are approximately 13,000 people living with AAV in the UK.
- We believe that in considering the economic model the Committee failed to give full weight to the savings in inpatient admissions and other healthcare costs resulting from improved control of the disease using rituximab. The full socio-economic benefits are probably impossible to assess meaningfully.
- We consider that this innovative biological technology, using targeted antibodies for the treatment of AAV represents the most important step change in the treatment of AAV since the introduction of cyclophosphamide forty years ago and this is a technology that will yield future benefits.
- We consider it to be wholly unconscionable that this valuable and proven new treatment should be denied to patients in the following categories. For these patients there is no alternative treatment offering anything near the same reliability or efficacy.

  1) As primary induction agent for those who are intolerant of cyclo-phosphamide or young females who wish to maintain fertility.
  2) As a secondary induction agent for refractory or resistant cases.
  3) As a secondary induction agent for cases of severe relapse as clearly defined in the BSR 2013 revised Guidelines for treating adult AAV.
  4) As a maintenance regime in cases where it can clearly be shown that stable remission cannot be induced using currently available immune suppressing drugs and where prolonged or repeated use of high dose steroids is to be avoided.
- We consider that the rejection by NICE of the use of rituximab in treating AAV will leave the UK out of step, lagging behind both Europe and the US in the treatment of this disease.

- We consider that this new technology is developing rapidly and reliable evidence is increasingly available (as recently as July 31st 2013) confirming the long term effectiveness and safety of rituximab. So in addition to those 4 applications described above, we believe that there should be opportunity for futher study of the routine use of rituximab as a primary induction agent and as maintenance treatment and further investigation of appropriate treatment protocols and the cost effectiveness of both of these uses.

- **Personal statement by Lisa Ranyell** (AAV sufferer & Patient Expert), who has experienced Rituximab treatment:-

  "After spending 2 years receiving the max dose of cyclophosphamide and methotrexate and permanently taking high dose steroids, I was given my first course of Rituximab in Dec 2008. 9 months later I was steroid free and have remained so ever since with no maintenance therapy other than Rituximab as and when B Cells repopulate. I have also had no hospital admissions since 2008"

- **Personal statement by John Mills** (AAV sufferer, chair of Vasculitis UK, Patient Expert):-

  "I contracted Wegener's Granulomatosis in 2001. I received initial induction treatment with IV pulsed cyclophos. Afterwards I was given azathioprine as maintenance treatment, but the disease immediately relapsed so I was given oral cyclophosphamide for a long period until mycophenolate was approved in 2006 and I changed to that. Now, 12 years post-diagnosis, I still take mycophenolate, but despite being symptom free, my ANCA biomarker remains high. With hindsight my disease would have been considered refractory, but in 2001 the only available effective re-treatment was repeat cyclophosphamide.

  In 2008 I contracted carcinoma of the bladder. Again, with hindsight I know I received well over the total cumulative dose of cyclophosphamide that is considered safe. The carcinoma was effectively removed after 2 surgical interventions which involved 2 inpatient admissions and 2 general anaesthetics. I have been given numerous cystoscopies and will remain indefinitely at risk of recurrence of the carcinoma. I am aware that I am also at indefinite risk of developing leukaemia and lymphoma due to my cumulative exposure to cyclophosphamide.

  In 12 years I have never been free of immune suppressing medication.
  I regard myself to be at serious risk of major relapse once mycophenolate has been completely withdrawn, as persistently elevated ANCA biomarker levels are considered to be predictive of higher risk of relapse.

  For me personally, the knowledge that rituximab was available for retreatment of relapse, with no further exposure to cyclphosphamide, was hitherto reassuring.

- **As chairman of Vasculitis UK**, I was patient representative on the BSR panel which reviewed the published treatment guidelines for treatment of adult AAV. I was in part responsible for prompting the update review.
  The revision which subsequently took place did so in the light of an emerging body of evidence of the effectiveness and safety of rituximab. The new pre-published guidelines embody use of rituximab as a core option.

- **As chairman of Vasculitis UK**, I was recently invited to sit as a patient representative on the new NHS England Rheumatology Specialised Services Clinical Reference Group (CRG). The use of rituximab for treatment of AAV was endorsed by NHS England. The revised BSR AAV guidelines are considered by the CRG to be a keystone element in the specification for commissioning of services nationally for treatment of all forms of vasculitis, including AAV.
- **A large number of patient personal experiences of rituximab** was included as an appendix to the original submission. These were, almost without exception, lyrical in praise of the beneficial effect they had experienced following use of rituximab. I have received more personal anecdotal experiences since then. Two just received today are shown below:-

Dear Mr Mills,

I'm writing to you with regard to my condition Churg Strauss Syndrome. For me this just manifests in my ears (at the moment anyway). I've been suffering for the past 8 years with granulation tissue in both ears. I've had many treatments in the past, including steroid injections in my ear drums, several operations, i.v. antibiotics, a course of cyclophosphamide to name a few! All of which work for a while and then my symptoms return. For the past two years I've been undergoing Rituximab treatment. I can't tell you the difference this has made to me. When I saw my ENT consultant last week he said that he has never seen me look so well. There was a vast improvement in both ears and I must say I really do feel well. Then I saw Dr Jayne (head of vasculitis Addenbrookes Hospital) who said that I would definitely reap the benefits of having a top up dose of Rituximab once a year. I understand from him that you are collating evidence from past patients of this drug. I would be absolutely devastated if this drug was no longer available to me. [redacted]

Hello John, I have both ANCA vasculitis (Microscopic Polyangiitis) and idiopathic pulmonary haemerosiderosis, which have affected me in the Lungs ,Heart ,Kidneys, Eyes and Stomach

Been on Rituximab since 2006 .Last year my IgG was playing up so Ritux it was stopped, put on IVIG and my B cells returned so was put back on Ritixmab every 6 months, it controls both of my illnesses, the respiratory consultant says that I am in a non recoverable position with my lungs. Without Rituximab I will expire. [redacted]

Supplementary Notes.

1) Until the introduction of cyclophosphamide forty years ago, systemic ANCA associated vasculitis (AAV), was invariably rapidly fatal. Cyclophosphamide was a step change in treatment and has saved thousands of lives. Unfortunately however it is extremely and indiscriminately cytotoxic and its metabolites are carcinogenic

2) Patients continue to die today because;-

   a) the disease is not recognised in time or
   b) is resistant to cyclophosphamide or
   c) they cannot tolerate cyclophosphamide or
   d) the disease relapses – cyclophosphamide has been shown to be less effective in cases of re-treatment.
   e) due to the numerous side effects of drugs used in treatment especially gluco-cortico steroids and untargeted immune suppressants
   f) due to irreversible organ damage prior to or in early stages of treatment or due to inadequate control of the disease process.
   g) Due to opportunistic infections as a result of immune suppression.

3) The decision **not** to approve the use of rituximab in the treatment of vasculitis is seen as a severe setback by those suffering from the disease and the effect of this decision is to create a predisposition against the use of this valuable new biological treatment.

4) For some, future fertility is an issue, especially females of child-bearing age, who frequently refuse to have induction with cyclophosphamide for fear of compromising their fertility. This can have serious consequences for their continuing health and survival and in some cases has resulted in unnecessary death.

5) As patients reviewing the use of rituximab in treating vasculitis we consider it to be of particular special benefit in three situations:-

   a) <u>As a **secondary** induction agent for those with refractory vasculitis</u>

      Systemic ANCA associated vasculitis is a variable, frequently aggressive disease which can progress very rapidly to cause death and permanent organ damage or destruction. In the case of lung involvement, death or severe disability can ensue. In the case of renal involvement, death or dialysis may be the result if effective treatment is not introduced. For those where cyclophosphamide proves inadequate to control the disease, a second line of treatment is essential.

      Failure to have rituximab available as a secondary induction agent for those with refractory AAV is seen as an extreme setback.

b) As a **primary** induction agent for those with fertility issues or for whom cyclophos is unsuitable for clinical reasons.

Failure to have rituximab available as a primary induction agent for this group is, we consider, a regressive step. Whilst sperm storage is relatively reliable and straightforward, harvesting ova prior to induction is invasive, unpleasant and not without hazard, especially for a young female patient who is seriously ill. The procedure may cause a delay in introduction of essential life and organ-saving treatment. The financial cost of subsequent in vitro fertilisation and implantation is significant. The personal cost is incalculable.

c) As a **secondary** induction treatment for treatment of severe relapse.

ANCA vasculitis is an incurable chronic disease. **All** people suffering from ANCA vasculitis are subject to relapse – around 50% within 5 years of remission. The threat of relapse continues indefinitely no matter how long a period of remission has been experienced.

Rituximab has been shown to be highly successful in treating relapse without causing the unpleasant and dangerous side effects associated with an indiscriminately cytotoxic drug like cyclophosphamide.

Anecdotal evidence from patients, which was included as auxiliary evidence in the original Vuk submission, suggests that following treatment with Rituximab, they experience a significant improvement in their quality of life. One might infer that this is due either to improved control of the basic disease or reduced side effects from maintenance drugs, especially prednisolone.

Removal of Rituximab from the range of available treatment options represents a very severe blow for all AAV patients. Rituximab has been perceived as the only major advance in treatment of AAV since the introduction of cyclophosphamide forty years ago. Whilst not quite the "silver bullet" that was hoped for, it is a step change in controlling this unpleasant disease.

Supplementary Evidence not available to the Appraisal Committee & ERG.

1) As chair of Vasculitis UK I was involved in the review process leading to the revision of the BSR Guidelines for treatment of Adult AAV. The introduction of Rituximab was a driving factor in the revision process.

Several of the questions that were raised at the appraisal committee meeting are answered in the revised guidelines. I understand that a pre-publication version has now been made available for committee members.

2) As chair of Vasculitis UK I am a member of the Rheumatology Specialised Services Clinical Review Group. The revised BSR guidelines embody treatment with Rituximab as a core treatment pathway for adult AAV. The use of Rituximab has been endorsed by NHS England.

3) The BSR Guidelines will be a core element of Service Specification for treating AAV. The total rejection of Rituximab as part of a treatment pathway will represent a major conflict for the CRG.

4) The treatment protocols for the use of Rituximab as described in the application are at odds with what we patients in the UK have experienced and were quite clearly also a source of confusion for the clinical experts present at the open meeting for the same reason.

5) Very recently published evidence from the US NIHR on 31/7/13 confirms longer term effectiveness of rituximab.

John Mills. August 2013