NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Rituximab in combination with corticosteroids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: John Mills

Name of your organisation: Vasculitis UK

Are you (tick all that apply):

✓ a patient with the condition for which NICE is considering this technology?

- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

✓ other? Chairman of the UK Vasculitis Trust (Vasculitis UK)

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What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

INTRODUCTION. About Vasculitis – a simplified overview.

Vasculitis is a systemic auto-immune condition causing inflammation of the walls of the blood vessels. This, in turn, causes blockage or partial blockage of those vessels. In the case of capillaries, it also causes them to become "leaky". This reduction in blood flow and leaking of blood into the tissues causes death and damage to the organs involved.

Vasculitis can affect people of any age from infancy onwards although the incidence of some of the individual types of the disease is predominantly in either older or younger age groups. Some types have a gender predominance. Some seem to have an ethnic or regional predominance.

Systemic vasculitis is potentially fatal. The 1 and 5 year survival rates for several types of vasculitis are worse than those for both breast and prostate cancer.

There are 18 quite different types of vasculitis, classified mainly by the size of the blood vessels affected (large, medium, small or a mixture). The disease can affect any organ in the body, often several. For example, loss of hearing, eyesight, digits or (rarely) limbs can occur; skin rashes are common; the central nervous system (brain & spinal chord) and the peripheral nervous system can be affected; there is frequently gastro-intestinal involvement; the heart can be involved. The disease is very variable indeed!

Vasculitis cannot be cured, but its progress can usually be controlled by the use of immune suppressing drugs. High dose steroids in the form of prednisolone are a first line treatment in stabilising the condition initially, but this only suppresses the inflammation and the disease remains active. When used alone, the high doses of steroids needed for long-term control of the disease can cause devastating side effects.

Thus, until the introduction of the potent chemotherapy drug cyclophosphamide for treatment of vasculitis it was an almost invariably fatal illness within a short period. Unfortunately some cases are still found to be refractory and do not respond to conventional treatment with a combination of steroids and cyclophosphamide.

However the most serious consequences result when the lungs or kidneys are affected. Capillary leakage in the lungs can cause patients to "drown in their own blood". Kidney damage can ensue as a result of blockage of the main blood vessels supplying the kidneys or due to damage to the capillary bed within the kidneys causing glomerulonephritis. In these cases patients frequently require dialysis, short or long term. Some require a kidney transplant.

Once the disease has been brought under control, usually by using cyclophosphamide (the induction phase), there follows a long period, maybe several years, of maintenance therapy usually using a combination of cortico-steroids (usually prednisolone) and immune-suppressing drugs. These all have their individual side effects, but most serious damage is probably caused by long-term use of cortico-steroids.

In more recent times, the "biologics" – manufactured monoclonal "targeted" antibodies have been used in clinical trials for the treatment of vasculitis, with varying degrees of success. Foremost among these is Rituximab, which targets the B cells. This has been found to be at least as successful as

cyclophosphamide for initial induction and better than cyclophosphamide for the re-treatment of refractory (which do not respond well to conventional treatment) and relapse cases.

In some patients, relapse can be a frequent occurrence and further organ damage can occur with each relapse. Thus the length of time between relapses and re-treatments is a highly significant consideration.

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology.

Many patients with vasculitis suffer from the long term effects of both the disease and side effects of the treatment. This is made worse by the fact that the disease is not easy to recognise, so frequently goes unrecognised and undiagnosed for long periods with progressing irreversible organ damage. Once diagnosed, the potential seriousness of the disease is not always fully appreciated, so initial treatment with less effective drugs is introduced. This may suppress the outward signs and symptoms and biomarkers but still allows the disease to continue sub-clinically, so rather than inducing remission, as soon as the medication is reduced or withdrawn, the disease relapses.

Given adequate and effective treatment, many patients recover sufficiently to return to normal or near normal life, but others are disabled in varying degrees by the permanent damage caused while the disease was active. This includes:-

- seriously impaired kidney function, possibly requiring dialysis or transplant;
- damage to the lungs and lower respiratory tract causing shortness of breath,
- damage to the upper respiratory tract causing collapse or even destruction of the nose;
- impaired hearing or deafness and loss of balance, due to damage to the auditory nerve and middle ear;
- partial or total loss of vision due to damage to the optic nerve;
- loss of mobility due to motor nerve neuropathy or vascular damage in the limbs
- chronic, sometimes severe pain, due to neuropathy of the sensory nerves.
- various other problems due to neuropathy of the autonomic nervous system
- lack of concentration and loss of memory, loss of mobility and incontinence due to damage to the central nevous system.
- Impaired blood supply in the gut can cause bowel ischaemia, sometimes necessitating removal of sections of the bowel
- Most patients suffer from severe fatigue of the type that is experienced by those with chronic kidney disease and suffering from severe cancer.

Many of these disabilities may be combined in one individual. This leads to poor quality of life and often renders them unfit for work or seriously impairs their employment prospects. This is particularly the case where there are frequent relapses of the disease.

The nature and consequences of the disease can have a profound effect on mental state, although many retain a positive attitude and strong sense of humour, that helps to combat the disease! However, others succumb to serious depression. Some of those who have received Rituximab suggest that it gives them an immediate psychological lift because they feel confident in the drug and its apparent relative lack of side effects.

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Coping with vasculitis, like many chronic disabling diseases, can put a severe strain on family relationships and friendships. Not all partners find themselves able to cope and friends and employers are not always as sympathetic as one might hope.

Thus any treatment that might improve the course of the disease and its outcome is greatly welcomed. All patients with vasculitis hope for the "magic bullet" that will cure the disease, or at least induce permanent remission. Both clinical trials and patient experience suggest that Rituximab is not the "magic bullet", but for many it has had a profoundly life-changing effect.

Appended to this submission are extracts from approx 25 letters from patients who have been treated with Rituximab, recounting their experiences. This anecdotal evidence forms an essential part of this submission.

In summary, the patient perception is that Rituximab:-

a) Can be instrumental in avoiding further organ damage.
b) Has less side effects than other remission inducing drugs
c) Is highly effective in both initial induction and treating relapse
d) Is effective in reducing hospital in-patient stays
e) Is effective in reducing exposure to cytotoxic cyclophosphamide.
f) Is effective in permitting reduced dependence of steroids
g) Produces longer periods of remission.

2. Disadvantages and problems

From the patient perspective, the disadvantages are as follows:-

- The treatment necessitates very slow infusion of the product under conditions of careful monitoring and control. Thus this usually indicates that it needs to be administered in centres with expertise and experience in its use, which may in turn involve travelling long distances and overnight stay. This obviously has practical and financial implications for patients who are not well and surviving on welfare benefits.
- It has, for some, not been easy to obtain this treatment for both regulatory reasons but sometimes apparently on grounds of cost. The outcome of this NICE appraisal might address that problem!
- There is substantial inconsistency between centres and clinicians about the situations where this treatment is most appropriate, how and when treatment should be applied and with what frequency; should Rituximab be given alone or in conjunction with other medication..This causes confusion. Whilst rigid guidelines are probably not appropriate for such a variable disease, some sort of more specific general guidance might be very valuable for those with less experience of its use.
- Patients receiving Rituximab do need regular careful monitoring in between treatments as the effects of the drug are variable and can be delayed. It can lead to sudden collapse in the White Cell count.
- The long term effects of the drug are not yet known.
- Close monitoring is required as Rtx can cause sudden drop in white blood cell count

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

Among patients, the value of this treatment is generally recognised and greatly appreciated.

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4. Are there any groups of patients who might benefit more from the technology than others? Are there any groups of patients who might benefit less from the technology than others?

Cyclophosphamide is a very potent and effective immune suppressing agent so highly effective for induction. However it is cytotoxic, so can have serious adverse effects on fertility of both males and females. Thus alternatives such as Rituximab should normally be considered for those who expect or intend to have children. Rituximab is highly effective in treating relapse and thereby avoids unnecessary repeat exposure to cyclophosphamide.

Rituximab should be the normal drug of choice for those who have shown serious side effects from cyclophosphamide and in retreatment of relapsed cases as the cumulative effect of cyclophos can be serious due to the effect of carcinogenic metabolites of cyclophos on the bladder. (I have personal experience of this)
This appears to be a cumulative effect so long term or repeat use of cyclophos is strongly contra-indicated.

Comparing the technology with alternative available treatments or technologies
Vasculitis is caused by aberrant activity of the immune system. By targeting only B cells, which are an essential part of the immune process, Rituximab is selective. By contrast cyclophosphamide is a powerful cytotoxic agent, which is potentially toxic to all cells, but especially those with a high level of cell division such as in the reproductive and immune systems. The carcinogenic effect is referred to above.
Cyclophos also causes hair loss and other unpleasant side effects.
Prednisolone is usually used in conjunction with cyclophos. Long term use of this can cause, most notably, diabetes, weight gain, cataracts and osteoporosis.

Induction treatment with drugs other than cyclophos (methotrexate, mycophenolate or azathioprine) is sometimes used in cases where the disease seems to be “limited” or less aggressive. However these regimes more frequently result in relapse when treatment is withdrawn or reduced, suggesting that control of the disease is only limited. Clinical trials show Rituximab to be very effective as an induction drug.

With all drugs, the aim is to have maximum therapeutic effect with minimum adverse or side effects. Both clinical trials and patient experience suggest that Rituximab compares very favourably on both counts.

Because of its efficacy, targeted pharmacological action, lack of side effects and long lasting effects, Rituximab is both steroid-sparing, generally less cytotoxic and shows a lesser relapse rate.

Use of Rituximab would seem to result in fewer hospital admissions, shorter hospital in-patient time, less frequent and less severe relapses. In consequence, despite the disadvantages described above, it results in better quality of life, less exposure to the side effects of cyclophosphamide and prednisolone and less dependence on maintenance with other immune suppressing drugs and their side effects.

My personal experience of over-exposure to cyclophosphamide was a carcinoma of the bladder which has resulted in 2 hospital admissions with surgical procedure under general anaesthetic, plus regular cystoscopy investigations to check for recurrence. These may continue indefinitely. The cost to the NHS of this must be many thousands of pounds.

Despite its initial expense and the need for administration in a hospital setting, Rituximab would appear likely to show net cost benefit to the NHS. Greater availability of Rituximab is likely to result in less cases like mine, described above. At present the use of Ritux is largely limited to re-treatments but if it was more

readily available it might become the treatment of choice for induction, with reduced exposure to cytotoxic drugs and steroids with their associated side effects.

<u>I would contend that a pre-disposition against the use of Rituximab is likely to result in higher than necessary mortality, unnecessary morbidity and unnecessary iatrogenic damage. This drug represents a very significant step forward in the battle against this group of rare and intractable diseases.</u>

A request was made to members of Vasculitis UK and those using the Vuk online discussion groups for people with experience of treatment with Rituximab to share their experiences for this appraisal. In an attempt to focus attention but without restricting freedom of expression unduly, the respondents were given a very simple template for guidance, as follows:-

1) Your pseudonym or other ID or other of your choice.
2) Place where you live – nearest town or city or county
3) Age now (not date of birth) Year when vasculitis first diagnosed
4) What type of vasculitis you are diagnosed with. WG; MPA etc
5) Brief details of how the disease affected you, what treatment you received initially (esp did you have cyclophos, if so was it IV or oral and for how long), how successful it was, did you have a relapse, did you have repeat cyclophos.
6) Were you given rtx right at the beginning (no cyclophos) or because the initial treatment did not work or because you had a relapse?
7) Date (approx) of first infusions & How many sets of infusions since
8) Were further treatments for routine maintenance or due to relapse.
9) What was good about your rtx & What was not good
10) Your personal assessment of rtx as a treatment for vasculitis, especially when compared to other treatments you might have experienced
11) The impact of rtx on your life and on your family.
12) Were you given rtx as part of a clinical trial or was it prescribed by your usual consultant.

There were 24 Respondents. All but 2 had cyclophosphamide initially.
Below are very brief extracts from some of these. To put them in context, please read the much lengthier extracts in the 12 pages appendix attached here.

1) "Since commencing treatment with Retuximab I have not experienced any side effects from it, I have not suffered with any symptoms of the disease, and without it I am sure that I would not be alive today".

2) "My experience of rituximab has been a good one. For me it has none of the unpleasant side effects I have experienced with the use of cyclophosphomide or prednisolone (such as sickness and weight gain) and has enabled a major reduction in the dosage of prednisolone I need to take. This in itself should provide me with longer term health benefits and has enabled me to lose weight and thus exercise more. In fact, the use of rituximab makes me feel for the first time in many years that I am on an upward, rather than downward, spiral in the management of my disease."

3) "Personal assessment is that it was a pain free treatment, it has given me a real hope of a extended period without troubles, rather than the Cyclophosphomide which was really just holding back the tide of my WG, and not so successfully, given the length of treatment and cost to body and organ function also. On my personal experience alone, I am so glad that my Drs went with this. I work full-time, I climb mountains, and I play football now despite legacy damage to kidneys, with proper diet I feel alive again."

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4) "My experience with Rituximab has been positive. It's more of a 'slow burner' so you don't see an instant improvement, but it does come and a few weeks later you slowly start to feel stronger and back to normal again. I found it less aggressive than cyclo. I had no side effects with Rituximab at all and I have continued to lead a relatively normal life and have continued to work throughout."

5) "Although the rtx as intended, knocked out my B cells, I didn't experience the hoped for boost of energy and improvement in my state of health, possibly because a lot of damage was done to me whilst waiting for a diagnosis in 2003 and rtx used when MMF lost it's benefit."

6) "I am single and look after my 97 year old mother - I obviously had fewer concerns about leaving my mother for the two RTX infusions than for the possible ten Cyclophosphamide infusions. I was also unable to care for her when I got such awful side effects with Cyclophos".

7) "Rituximab has improved my life massively as I feel more energetic and upbeat and have been able to reduce my steroids, which has improved my health with a weight loss. I am able to look after my grandchildren and enjoy life more."

8) "As you can see, I have previously had all the standard treatments but for me rtx has given me my life back and enabled me to forget to a certain extent about having WG and have a decent quality of life, able to work and enjoy my spare time."

9) "I consider Rituximab to be the best drug available to treat WG as it spares patients from suffering from horrific side effects caused by drugs such as cyclophosphamide and leads to a much better quality of life".

10) "For my wife and family I think the most remarkable result of the Rituximab is that there is a light at the end of the tunnel, whereas before we were struggling to find the tunnel and that we now feel a sense of normality slowly returning, which has been missing for some time in our home".

11) "It (rtx) has transformed my life without a question! Well I had a baby and wouldn't have been able to if I was on Mycophenolate."

12) "Rituximab has been miraculous as far as I am concerned and I bless it daily. I have no need of dialysis as my kidneys are sufficiently recovered to make this unnecessary".

13) "The only side effects I noticed ws fatigue, but my steroid dose had been increased at this time, so which is to blame?".

14)" I felt so unwell with cyclophos that changing to Rituximab was a blessing plus the blood markers said it was working, bit I still had the problem in August 2012."

15) "I feel it is an excellent treatment, no side effects, safe and far better than other treatments. Cyclophosphamide made me feel very ill. Ritux has allowed me to feel better and certainly more healthy."

16) "Personally, i think it is essential for people who have major flare ups as it did put mu WG into remission. It has made changes to my life , I feel much better and it has allowed me to reduce my meds."

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17) "The inflammation reduced very quickly after Ritux and I am now on fewer steroids than I have been on since diagnosis. It is 9 months since the Ritux infusion and I feel better than I have felt since the start of the illness. I won't be running any marathons any time soon, but I feel as though I have a life again."

18) "As a young female, age 25, I am grateful that I had the chance to be given a different drug that would not affect my fertility. Due to the effectiveness of rituximab in maintaining remission, I have been able to get my life back".

Appended below find anonymised extracts selected from all 25 separate letters received from patients, describing their experience of treatment with Rituximab – both good and bad! These extracts put the quotations shown above in their broader context. The unabridged text of the original letters (anonymised) is available on request.

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:
- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Other Issues
Please consider here any other issues you would like the Appraisal Committee to consider when appraising this technology.