NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Everolimus for preventing organ rejection in liver transplantation

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

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation Freeman Hospital NHS Trust

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? √
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Liver Transplantation is the mainstay of treatment for patients with ESLD and has a short and medium term success rate better than other organ transplants, with 90 day, 1 and 5 yr survival expected to be in the region of 95%, 90%, 85% respectively. But while short term survival after liver transplantation has notably improved in recent years, there remains a significant need to improve long-term survival.

Ojo et al, in a population-based cohort study, estimated that after 5 years, 18.1% of liver transplant recipients suffered from chronic renal failure and were at higher risk of death after transplant (relative risk: 4.55). This study was done in 2003 and since then over the last 10 yrs more and more Liver Transplant recipients are developing renal dysfunction. There is no doubt that the combination of Immunosuppression and CLD with high MELD/UKELD score is associated with significant morbidity.

The consequences of renal dysfunction in the early postoperative phase are very serious and influence poor outcomes and progressive renal failure, with increased risk of death. Causes of progressive kidney disease in a liver transplant setting are multifactorial, but CNI treatment has been recognized as a principal culprit. In the UK this is mostly Tacrolimus.
Current strategies for immunosuppression in liver transplant recipients take into account the risk of renal failure, hepatitis C, cardiovascular complications, and cancer – de novo or recurrent.

Everolimus can be used to spare the CNI and thus reduce toxicity and renal dysfunction and the mTOR effect can reduce the risk of malignancy.

Any new immunosuppressive drug, for liver transplant, should not have the toxicities associated with CNIs and should not have an adverse impact on hepatitis C virus (HCV)

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recurrence. These agents should also be able to minimize the risk of hepatocellular carcinoma (HCC) recurrence.

Everolimus, with its specific therapeutic effects, is believed to have some of these qualities. Early evidence suggests that the mTORi, everolimus and sirolimus, may offer effective immunosuppressive activity, together with less nephrotoxicity, and may cover unmet needs in long-term therapeutic management of the liver transplanted patient.Data relating to the administration of mTORi come mostly from kidney transplant patients, whereas experience
of mTORi after liver transplant is rather limited. Initial studies, which were published years ago, were inconclusive and raised concerns about their toxicities but new evidence is focused on the
effectiveness of everolimus, after liver transplantation, maximizing graft and patient survival, and minimizing the risks of adverse events and avoiding known risks associated with CNIs.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

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More recent data does reflect real life

The side effect profile is significant but manageable – and with patient engagement will be better tolerated

Equality and Diversity

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

None

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Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

Currently available on name patient basisis

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