

Clinical Commissioning Policy Statement

Rituximab for the treatment of refractory Focal Segmental Glomerulosclerosis in the native kidney in adults (1818)

Commissioning Position

Summary

Rituximab for refractory glomerulosclerosis in the native kidney in adults will not be routinely commissioned by NHS England.

Information about refractory glomerulosclerosis

The intervention

Many diseases and conditions can affect kidney function by attacking and damaging the glomeruli, the tiny filtering units inside the kidney where blood is cleaned. Focal Segmental Glomerulosclerosis (FSGS) is a type of glomerular disease and describes scarring (sclerosis) in the kidney. The scarring of FSGS only takes place in small sections of each glomerulus, and only a limited number of glomeruli are damaged at first.

FSGS affects both children and adults. Males are affected slightly more often than females. It is a rare disease but a relatively common cause of nephrotic syndrome. Nephrotic syndrome is a condition when the kidneys leak protein from the blood into the urine. As the body tries to compensate for this protein loss it leads to complications such as swelling, infections and developing blood clots. If FSGS is left untreated it can lead to kidney failure and the need for dialysis or transplantation.

The two types of FSGS are:

Primary or Idiopathic FSGS: The FSGS happened on its own without a known or obvious cause.

Secondary FSGS: This type is caused by another disease or a drug. Examples include viruses (e.g. HIV), drugs (e.g. anabolic steroids) or diseases such as diabetes. Current treatment for FSGS is usually steroids. If these do not work they can be followed by drugs that affect the body's immune response. There are some patients whose condition may continue to worsen even with these medications.

Rituximab is a drug that works by reducing the level of some of the cells in the immune system which may be attacking the body's own tissues.

The policy considers treatment in adults who still have their own (native) kidneys and not a transplanted kidney(s).

Committee discussion

The condition

FSGS may have no symptoms in its early stages. The course of the disease can vary greatly between individuals. FSGS is a leading cause of nephrotic syndrome accounting for 10-25% of

OFFICIAL

cases. Symptoms of nephrotic syndrome include oedema, weight gain due to fluid retention, high cholesterol and low levels of protein in the blood. In complex cases patients can also suffer with hypertension, anaemia and thrombosis.

Current treatments

A range of treatments are used for FSGS including corticosteroids and immunosuppressants, plasmapheresis, anti-hypertensives (including ACE inhibitors), and diuretics. Patients may also be required to make dietary changes.

Comparators

The evidence for Rituximab consists of case reports and case series. No direct comparison of clinical effectiveness was made against standard care.

Clinical trial evidence

NHS England has considered the evidence submitted as part of the preliminary policy proposal to establish the clinical commissioning policy statement, including the clinical criteria for initiating and discontinuing the intervention. This includes up to three of the most clinically impactful publications, identified using a literature search strategy defined by the clinical lead. These publications are summarised below.

Basu B, Mahapatra MD, Mondal MD. Mycophenolate mofetil following rituximab in children with steroid resistant nephrotic syndrome. *Pediatrics*, Vol 136, Number 1, July 2015

This study was a retrospective analysis of 24 children with refractory idiopathic steroid resistant nephrotic syndrome (SRNS). Follow up was 24 months. Children were treated with an initial course of 2-4 infusions of rituximab and at 3 months follow up received a second course of the drug along with mycophenolate mofetil (MMF). 40% of the children (11/24) had FSGS. After the initial course of treatment 21% of children (5/24) had complete remission. Only one of these children had FSGS. 4/5 of these children relapsed at a median interval of 53 days (range 46-72 days). 15 children started MMF at 3 months. By 24 months 33% of children sustained a complete remission after MMF maintenance therapy compared to rituximab therapy alone ($p < 0.001$).

The study had very small numbers of patients with even smaller numbers in each sub-group which may cast doubt on the applicability of the statistical analysis. There was no comparator group to assess effectiveness compared to best practice. A retrospective design increases the risk of selection bias and recall bias and may not adequately control for potential confounding factors. Patients were given varying doses and regimen of rituximab and had differing levels of exposure to previous therapies. The study was conducted in children which limits its applicability to adults.

Bagga A, Sinha A, Mougdil A. Rituximab in patients with steroid-resistant nephrotic syndrome. *Correspondence. N Engl J Med* 356;26 (June 28, 2007)

This case series describes five children with steroid resistant nephrotic syndrome (SRNS), two of whom had FSGS. All children had previously received multiple different medications (including calcineurin inhibitors) for varying periods with episodes of partial or complete remission. Participants received a rituximab infusion and continued on calcineurin inhibitors, prednisolone or both. At six months complete remission was maintained in three patients with tapering of steroids and calcineurin inhibitors.

OFFICIAL

It is not clear from the study whether the patients with sustained remission were those with FSGS. This is a small descriptive study but the population being studied had differing baseline characteristics, exposure to previous medications and duration of disease. The study was conducted in children which limits its applicability to adults.

Varwani MH, Sokwala A. Treatment of steroid resistant focal segmental glomerulosclerosis with rituximab: a case report and review of the literature. Saudi J Kidney Dis Transpl 2017; 28 (5): 1175-1179

This case report was of a 76 year old male with steroid resistant FSGS who was treated with rituximab and remained in remission at 6 months.

The patient remained oliguric (low urine output) for the next six weeks, requiring intermittent haemodialysis (HD) on an outpatient basis. On the 7th week following unsuccessful treatment of FSGS with steroids, the patient start treatment with rituximab. This was given at a dose of 375 mg/m² every two weeks for a total of four doses.

Following the first dose, a significant improvement in renal function was noted with an increase in urine output and reduction in proteinuria.

The patient had his last session of HD three days following the 1st dose of rituximab. Prednisone was tapered off. Three months later, he remained free of dialysis with a creatinine level of 125 µmol/L and proteinuria of less than 500 mg in 24 hours.

A case study is useful for generating a hypothesis and this is an adult patient but the study design and outcome has limited value in proving efficacy.

Adverse events

Rituximab is a licensed treatment for autoimmune diseases such as rheumatoid arthritis and ANCA associated vasculitis, where it has an excellent safety profile. None of the studies reported significant side effects in patients.

Implementation

Criteria

Not applicable.

Effective from

July 2019

Recommendations for data collection

Not applicable.

Mechanism for funding

Not applicable.

Policy review date

This is a policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation

OFFICIAL

has not been undertaken. If a review is needed due to a new evidence base then a new Provisional Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

It is noted a new NIHR trial - "TURING" will fund an RCT to address the lack of evidence of rituximab for both minimal change disease and FSGS in adults.

<https://www.fundingawards.nihr.ac.uk/award/17/83/06>

Links to other Policies

None.

It is noted NHS England routinely commissions treatment with rituximab for children with various forms of nephrotic syndrome, including FSGS as one of the causes of nephrotic syndrome in children. However, the Policy Working Group when considering the scope of this policy and the published evidence took into account the heterogeneity of nephrotic syndrome and FSGS and differences in causation in adults and children that make comparisons across the evidence base difficult.

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.