NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Bristol Myers Squibb

Belatacept
Executive Summary

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Renal transplantation is the preferred treatment for End-Stage Renal Disease (ESRD) because it confers improved survival and quality of life compared with dialysis. Following transplantation, recipients require lifelong immunosuppression to suppress the alloimmune response and maintain a functioning graft.

Belatacept is a first-line non-nephrotoxic immunosuppressant, with an improved cardiovascular (CV) profile compared with the calcineurin inhibitor (CNI) ciclosporin. It belongs to a new class of therapeutic immunosuppressive agent that differs from existing immunosuppressive agents not only in its mode of delivery (intravenous [IV] infusion) but also in its narrower range of molecular targets leading to a greater specificity of clinical effect.

Clinical evidence

The key clinical evidence for belatacept presented in this submission is drawn from two randomized, partially-blinded, active-controlled, parallel group, multicentre phase III studies designed to directly compare belatacept with ciclosporin as a first line maintenance immunosuppressant in adults receiving a renal transplant from either a low risk, standard criteria donor (SCD) (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial [BENEFIT]) or a high risk, extended criteria donor (ECD) (Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial-EXTended criteria donors [BENEFIT-EXT]) up to 36 months post-transplantation.

Safety and tolerability data from BENEFIT and BENFIT-EXT as well as long term extension studies demonstrate that belatacept is safe and well tolerated. Trial data from BENEFIT and BENFIT-EXT demonstrated the following:

- Belatacept has comparable rates of patient and graft survival from transplantation at month 12 and month 36 in both BENEFIT and BENEFIT-EXT when compared with ciclosporin.
- Belatacept demonstrated a greater preservation of renal function (assessed by glomerular filtration rate [GFR]) and renal structure (assessed by the prevalence of chronic allograft nephropathy [CAN]), when compared with ciclosporin.
- Preservation of renal function was observed despite higher rates and grades of early acute rejection with belatacept than ciclosporin.
- Belatacept is associated with better CV and metabolic risk profiles relative to ciclosporin.

Belatacept may also provide an additional benefit in terms of a reduction in the development of antibody-meditated rejection, as in both BENEFIT and BENEFIT-EXT observed rates of donor-specific anti-human leukocyte antigen (HLA) antibody production were lower in belatacept-treated patients versus ciclosporin-treated patients; although the clinical importance of this observation requires further investigation.

Economic evaluation

The submission assesses the cost-effectiveness of belatacept within its licensed indication compared to current standard of care of ciclosporin or tacrolimus from the perspective of the NHS as payer. The base case focuses on the combined results from Phase III trials, BENEFIT and BENEFIT-EXT, which are integrated into a published model that projects long-term graft and patient survival after transplantation (Levy *et al*. 2014).[1]

The base case analyses demonstrated that, whilst belatacept resulted in an increased expenditure (£92,216 and £91,001 more than ciclosporin and tacrolimus, respectively), it provided patients with, on average, 0.97 and 0.62 more quality-adjusted life years, respectively. The resultant incremental cost-effectiveness ratios (ICERs) were £95,053 and £147,334, respectively. Deterministic sensitivity analyses demonstrated that ICER values were most susceptible to changes in graft-survival and the price of immunosuppression, whilst being relatively unaffected by changes to disease state cost and utility estimates.

Additional analysis was conducted in recipients of ECD organs with reduced kidney function (determined by GFR). In this subgroup, belatacept was dominant compared with both ciclosporin and tacrolimus, producing observed ICERs of -£3,237 and -£9,126, respectively. Quality-adjusted life expectancy was also improved compared to ciclosporin and tacrolimus by 0.46 and 0.46 years respectively.

As the dose of immunosuppressants is weight-based, further scenario analyses explored the cost-effectiveness of belatacept in patients that fall into higher weight categories at dosages recommended in comparator's product Summary of Characteristics (SPCs) and the British National Formulary (BNF). This resulted in a significant reduction in ICER values when comparing belatacept with ciclosporin and tacrolimus. Results estimated that belatacept would be cost-effective at the £30,000/ quality-adjusted life year (QALY) threshold in patients weighing over 89 kg and receiving the lower limit of recommended tacrolimus dosing; and dominant in all weight categories against patients receiving the upper limit of recommended tacrolimus dosing.

Conclusion

The maintenance of post-transplantation GFR has emerged as the strongest determinant of long-term graft survival, CV events and transplant recipient mortality. Treatment with belatacept significantly increases post-transplantation GFR, which has been associated with increased graft-survival in clinical trial data shown to date.

The economic evaluation has demonstrated that belatacept is unlikely to be cost-effective when implemented across the entire renal transplant recipient population. However belatacept is likely to offer a cost-effective treatment option when implemented in recipients of ECD kidneys, or in those who are anticipated to have low kidney function (GFR) post-transplantation and are likely to have low graft survival and return to dialysis. In addition belatacept may also be cost-effective in those with in higher weight categories, or in those that requiring higher doses of immunosuppressant medication.