12/02/17

**Marketing strategy for a novel biologic treatment for ischaemia-reperfusion injury in organ transplant**

The Market

Ischaemia-reperfusion injury (IRI) is the inflammatory response-mediated organ damage that occurs when blood supply to a part of the body is temporarily cut off and then restarted- such as in organ transplantation or cardiac infarction1. In the case of organ transplantation, primary graft failure related to IRI is the second greatest cause of rejection after immunological rejection, with 5-15% of patients suffering primary graft nonfunction and 10-25% of patients suffering from initial poor function2; IRI is also associated with short and long-term problems with the transplanted organs3. In the USA, total medical costs for solid organ transplant per patient range from over $330,000 for a single kidney to over $1.5 million for intestine4, so preventing primary failure and the ensuing need for re-transplantation is highly desirable from a financial standpoint, before even considering the detrimental effect on patient health from the physical and emotional trauma of repeated transplant operations. Over 100,000 single organ transplants are performed worldwide annually5, which is only around 10% of the actual need for organs6; this extreme shortage has led to widening of donor criteria and more marginal organs being accepted for donation, with such organs being more susceptible to IRI7. It is therefore essential to minimise the risk of IRI to improve organ acceptance and the chance of long-term success. Assuming the primary graft nonfunction and initial poor function numbers carry through to all solid organ transplants, anywhere between 5,000 and 25,000 patients could benefit from IRI prevention annually; however, as it is not yet possible to predict which patients and organs will suffer from a clinically-significant IRI, an effective preventative strategy is likely to require blanket treatment of all organ recipients, boosting the patient numbers. Although a number of solutions have been proposed, none have entered the clinic to date8. There is therefore an underserved, high-stakes market desperate for an effective prophylactic treatment for IRI.

The product

We have recently developed a fusion protein biologic, Rohumein, that has been shown to induce hepatocyte proliferation in the liver of mice and pigs. In an ischaemia-reperfusion experiment in mice, those pre-treated with two doses of vehicle (24 and 12 hours before ischaemic insult) showed significant reperfusion injury, including substantial endothelial cell death, while those pre-treated with Rohumein not only remained uninjured, but showed healthy hepatocyte proliferation and vascular structure. This effect was repeated in a pig IRI study, and a Phase I human trial showed the protein to be safe and well-tolerated in healthy subjects. A similar study was carried out in mice for kidney IRI and was also successful. Rohumein is a fully human form of a protein already present in the circulation fused with human Fc, and is therefore less likely to cause an immunogenic reaction.

Rohumein is an injectable biologic, but as the patient population of organ recipients is already hospitalised with intensive medical intervention, there are no foreseen issues with delivery and compliance. The pre-treatment time of 24 and 12 hours before transplant fits within the acceptable time window of liver survival outside the body9, and thus could begin as soon as a suitable organ is found without compromising the chances of success. This would require Rohumein to be kept in stock at hospitals performing these procedures, but as the protein has been found to be highly stable at 4oC for up to two months and -20oC for over one year, with no unacceptable levels of aggregation or deterioration of activity in those time frames, this should not cause any difficulties. The optimal dose in pigs is 0.75mg/kg, and doses of up to 3mg/kg have been well-tolerated in Phase I human trials; the expected optimal human dose is 1mg/kg.

Financial plan

The drug was discovered in an academic laboratory, with further development jointly funded by us and a research council, so pre-clinical out-of-pocket costs for us were substantially lower than the $2.6M costs estimated by Horvath10. Due to the intense interest in improving outcomes from organ transplants worldwide, it should be possible to receive support in Phase II/III clinical trials from charities, government, and healthcare payers. Due to the relatively low patient numbers, we qualify for orphan drug designation11, which speeds up the approval process and allows for smaller (and thus cheaper) clinical trials. in the USA, orphan drugs are eligible for up to $30M in R&D grants for Phase I-III trials, and receive a 50% tax credit on R&D costs12. With these credits, a Phase III trial for orphan drugs costs on average around $50M, compared to nearly $200M for non-orphan drugs12. In both the USA and Europe, the fees associated with the regulatory approval process are also reduced for orphan drugs12,13.

A logistically-similar biologic pre-treatment trial is currently taking place in the US with Remicade, and following this already-approved format could save time and money in trial design14.

QA costs could potentially be higher for this drug as it will be going to very ill and immunocompromised patients, so very robust quality control and analytical programmes will need to be in place to guarantee the highest standards. These can be very costly, but are easy to justify when setting pricing.

Intellectual property strategy

A patent application has been filed for Rohumein for prevention of IRI in organ transplant in humans and companion animals. Interestingly, there is a growing market for companion animal transplants15, specifically dog and cat kidney transplants. This could also provide an alternative early entry market for Rohumein, as the regulatory barriers for the veterinary market are substantially lower.

Orphan designation provides seven years of market exclusivity from FDA approval, and ten years from EMA approval, automatically extending the life of the patent. In Europe we may also have scope to apply for a Supplementary Protection Certificate to extend the life of the patent by another 5 years.

There may also be applications for this drug in other forms of IRI, such as stroke, cardiac infarction, pressure wounds and crush syndrome, and preclinical studies indicate a benefit; we have filed for these indications as well. In these cases, rather than a prophylactic, Rohumein would be a treatment measure after the fact. This would require a new research programme, but the large patient numbers affected would make the investment extremely worthwhile.

Marketing strategy

This drug is unlikely to benefit significantly from mass marketing approaches, due to the small patient population. Some direct marketing in the form of literature that can be added to a patient information packet might be beneficial, but is unlikely to have much impact if transplant surgeons are not already in favour of its use. The most successful strategy is therefore likely to be targeting medical professionals and transplant charities, with the ultimate goal of embedding Rohumein in the standard care at the time of transplantation. Should this occur, reimbursement should not be an issue, as Rohumein will be the ‘gold standard’ treatment for preventing non-immunogenic organ rejection. However, it is essential to begin working with payers now to determine the value of IRI prophylaxis to them. For a system such as the NHS, the patient numbers are very small, but the potential benefits are very large if more transplants are successful. For a private system like the US, where the overall costs to an insurer are in the hundreds of thousands to over a million dollars per patient, a drug that reduces the chance of needing another transplant due to primary failure would be of high value.

With over 100,000 transplants each year around the world and demand only likely to increase, the market is stable with growth potential. Due to the high risk profile of organ transplant patients, this is an indication that is most likely to benefit an originator molecule substantially more than any future biosimilar. The patient population is probably too modest to justify the costs involved in replicating clinical data in this patient population and trying to compete against the originator is unlikely without intensive, expensive marketing and large price reductions to make the biosimilar sufficiently attractive as a replacement. A smart pricing strategy will also help keep competitors at bay, as clinicians will have little motivation to seek out biosimilars if Rohumein is seen as cost effective. As this drug has been licensed in rather than being part of a discovery programme, costs for related failures do not need to be recouped in the price, and marketing costs are also likely to be low with the strategy outlined above. Given the incentives for orphan drug designation, we calculate the total cost to approval plus marketing to be around $200M, which would need to be reimbursed before any profit can be made. The US market is likely to be the most profitable entry market, with an annual recipient population of over 30,00016. If Rohumein were given to all of them, a cost of only around $7000 per patient would allow R&D, approval and marketing cost recovery in one year. As mentioned above, keeping the price low has a number of likely long-term benefits, so the target price range for the US market, also factoring in manufacturing and QA costs, will be $2500-5000 per dose with a two-dose treatment regimen. For the UK, we will work with NICE and the Scottish Medicines Consortium to determine reimbursement, but expect that a comparable price range will be acceptable as transplants are considered cost-effective, and this would be a one-off cost per patient rather than the continuous cost of post-operative immune-suppressing drugs. For future sales in developing countries, a rebate or cost-reduction strategy will probably be required.

There may also be a benefit to treating the donor with Rohumein prior to removal of the organ, and cases such as live organ donors and patients being kept on life support for cadaver donation would provide sufficient notice for the treatment window. This could increase the patient population, but would require additional trials. It is possible that physicians may realise the potential of Rohumein for other forms of IRI and prescribe it off-label. While we clearly could not market these off-label uses for ethical and legal reasons, such uses would increase sales and provide a body of evidence to justify future trials and eventual marketing for those uses.

SWOT analysis:

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| **Strengths** | **Weaknesses** |
| * Modified form of naturally circulating proteins, unlikely to cause immunogenic reaction * Clearly defined patient population * Effective in large animal (pig) model * Well-tolerated in human Phase I trials | * Small, high-risk population can make clinical trials difficult * Very high QA costs to ensure safety of immunocompromised patients * High cost of manufacture compared to small molecules |
| **Opportunities** | **Threats** |
| * Orphan designation reduces risk and offers 7-year market exclusivity * High barrier to entry for biosimilars protects market share * Off-label prescription by physicians may increase sales and justify new trials for other indications * Companion animal transplants may offer an addition opportunity with lower regulatory hurdles | * May find that efficacy will not sufficiently justify cost * Surgeons may be sceptical * Payers may be unwilling to add cost to already-expensive procedure * Adverse reactions in already very sick patients could be disastrous |

Conclusion

Rohumein is a fusion protein biologic with potential as a prophylactic and/or treatment for ischaemia-reperfusion injury. By targeting IRI in organ transplant, Rohumein qualifies as an orphan drug, which brings significant financial and logistical benefits for its clinical development. Should it prove successful in Phase II/III trials and get approved, we will aim to make it part of standard pre-operative treatment for organ recipients, at a price point that allows for a profit within two years of release but remains low enough to encourage uptake and discourage future biosimilar competition.

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