University of BRISTOL

Elizabeth Blackwell Institute for Health Research

Elizabeth Blackwell Institute Research for Health Scheme 2015

Stage 1 - Call for Challenges Application Form

Challenger	Charlotte Bradbury
Challenge Title (max 20 Words)	
Predicting patient responses to immunosuppressive treatment in autoimmune thrombocytopenia (ITP)	

Please describe the specific problem which needs addressing
Immune thrombocytopenia (ITP) is an autoimmune illness that presents with bruising and bleeding due to a low platelet count (blood cells that are essential for normal clotting). Bleeding can be life threatening and does not respond to platelet transfusions. There is increased consumption and reduced production of platelets due to both antibody and cell mediated autoimmune attack of platelets and megakaryocytes (platelet producing cells). Annually in the UK there are 1800 new diagnoses of ITP (30 per year in the adult non-malignant haematology practice at University Hospitals Bristol). In approximately 80% of these new diagnoses, there is sufficiently high bleeding risk to initiate disease-modulating immunosuppressive therapy (UK ITP registry data). Best practice clinical guidelines currently recommend that the first line therapy for ITP is high dose corticosteroids with a reducing dose over 1 to 3 months. The standard first line treatment with steroids has not been challenged for decades and there are three big downsides, steroid side effects, heterogeneity of response and high relapse rates when they are stopped. Steroids are associated with side effects including difficulty sleeping, weight gain, mood disturbance, high blood pressure, diabetes, gastric irritation and osteoporosis. In the UK ITP registry, data collected from 1432 patients revealed that steroid related comorbidities were the

most frequently reported (hypertension in 30%, diabetes in 19%) and correlated with duration of treatment (Newland A et al, BSH 2015 presentation) confirming the significant side effect burden of these agents. A patient survey has also revealed steroids to be associated with more side effects than other therapies used for ITP (Brown et al 2012).

A further major limitation of high dose corticosteroids is that patients with ITP are highly heterogeneous in response with a proportion of patients who don't respond at all (approximately 20% are refractory).In those who do respond, the response is variable and there is a high relapse rate (up to 90%) when steroids are stopped. Patients who are refractory to steroid or relapse are at risk of severe bleeding including intracranial haemorrhage. Disease activity is also associated with fatigue which is occasionally disabling. Physical factors combine with psychological stress (e.g. fear of bleeding and uncertainty of disease outcome) and social difficulties (need for time off work or school, lifestyle restrictions due to bleeding risk) to adversely impact on quality of life. Patients in this group require monitoring at least weekly until a stable platelet count is achieved with an alternative therapy. At UH Bristol, over 3 months there were >100 day unit attendances for patients with ITP (over and above clinic appointments). This represents a significant burden for patients and the health care facilities that they use. ITP thereby represents the most impactful chronic non-malignant haematology disorder in our practice.

Patients who are poor responders to steroid (refractory of relapsed) are generally commenced on second line immunomodulatory treatments including cyclosporine, mycophenolate, azathioprine or rituximab. Unfortunately, all these treatments are slow acting with a lag period of up to 2 months before maximal effect. In the interim period patients are at significant risk of bleeding and may receive a further dose of steroids to "bridge the gap" or other rescue treatments such as IVIG and continue to require weekly monitoring with disruption to patient's lives and burden on healthcare resources.

The main challenge for clinicians who manage patients with ITP is to improve the efficacy and safety of current treatment pathways by selecting the optimum therapy as close to diagnosis as possible. At present, all patients receive high dose steroids at diagnosis. However, it is clear that for a significant proportion of patients these are unsatisfactory. Feedback from a patient group in Bristol has clarified that steroid side effects, relapses and time off work are the most troublesome problems that face patients with ITP. Predictive laboratory measures of steroid responses are urgently needed to help individualise treatments, ensuring that only the patients likely to respond to steroids have to suffer the side effects, while an alternative treatment is chosen promptly for those that are unlikely to respond. There are similar challenges in other autoimmune disorders such as posterior uveitis, inflammatory bowel disease and hepatitis. However in these disorders it is already known that examining the proliferative response of lymphocytes to corticosteroids ex vivo enables identification of a subgroup of approximately 30% of patients who are corticosteroid resistant[1].

The main research challenge in my non-malignant haematology practice is to determine whether this experience in other autoimmune disorders can be extended to develop a robust and reliable predictive clinical test for corticosteroid responsiveness in ITP.

How does this issue impact on you, your colleagues and your patients?

The current practice of prescribing corticosteroids as first line treatment for all new patients with ITP, followed by watch-and-wait before switching to second line immunomodulatory drugs in poor responders is highly impactful for patients and health services.

The possibility of advancing the clinical decision of whether to switch to second line therapy very early in the treatment course has several major impacts;

1. Selecting the best early treatment for each ITP patient on an individual basis is likely to improve the overall success of treatment by minimising the time period at which patients have dangerously low platelet counts (reducing time to remission and reducing likelihood of relapse).

2. Avoiding unnecessary treatment with corticosteroids in patients who are unlikely to respond will minimise the overall toxicity of immunosupressive treatment and improve quality of life.

3. Together, these potential efficacy and safety improvements will reduce the impact of ITP on NHS resources by reducing the costs associated with frequent patient contacts for monitoring and interventions to reverse toxicities.

4. If this clinical problem is solved in ITP, then the approach is likely to be applicable to a broader range of autoimmune disorders which collectively are a major source of morbidity and mortality for NHS patients (prevalence of 3%).

Can you estimate how many patients or staff are affected by this problem?

Can you describe any associated financial implications for the NHS or patients?

(Don't worry if you are not able to answer this question at this stage – it is not compulsory)

Development of a laboratory test to predict corticosteroid responsiveness will potentially impact on all the 1800 new cases of ITP annually in the UK. This issue is relevant to all acute NHS trusts.

References

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