STRESS-L Current Evidence

Why is this trial important?

At the heart of STRESS-L is a mechanistic study with outcomes that *matter* to patients

Background

Beta blockers are some of the most widely studied drugs. Ever since Sir James Black [1] discovered a drug to block the β2 receptor, drug companies have been designing molecules to separate out their effects on various tissues. In general, β1-receptors predominate in the heart whilst β2-receptors are widely distributed mainly found in smooth muscles such as vessels and bronchus.

The role on the immune system is less well studied and an important part of STRESS-L is to begin to study some of the pathways and mechanisms affected by β1 blockade. A major problem for us in putting this hypothesis together are the models that have previously been reported. Reports of changes in cytokines in a cell model are not always transferrable to our patients. Don't forget - the type and concentration of cytokines varies over the course of the sepsis; anti-inflammatory cytokines are just as important as pro-inflammatory, as they wind down the immune system once the infection has been dealt but these may be harmful if started too early. Animal models vary widely having studied differing species (mouse, rat, dog), sepsis stimulus (lipopolysaccharide, caecal ligation and puncture), beta blocker type (propranolol, metoprolol, esmolol, landiolol), timing and outcome (cytokine change or mortality).

Hypothesis

Catecholamines reduce pro-inflammation through β2-receptors on neutrophils and upregulate synthesis of anti-inflammatory cytokines (for example, IL-10). Landiolol may therefore unmask the β2 effects and make the immune system more active. We are therefore measuring cytokines over the course of STRESS-L up to the end of noradrenaline treatment. Interestingly, one study has even suggested that there were three times more β2-receptors on neutrophils from females than males which may mean that there is a sex difference between responses [2]. We are particularly interested in patients who receive beta agonists such as dobutamine or adrenaline; these patients are exceptionally vulnerable and are a high mortality risk [3]. (As a reminder, the high mortality in these patients means that unless there is an active withdrawal process in place, we are still keen for these patients to be screened).

Most lymphocytes and macrophages (monocytes) express β-adrenergic receptors on their surface, with the exception of T-helper type 2 (Th2) cells. Lymphocytes are susceptible to stimulation by adrenaline, so that they differentiate into mature macrophages that are functionally different in their cytokine response. So, for example, the macrophage response might be important in clearing

damaged bacteria or cells during the resolution of sepsis but not so important earlier in sepsis where finding and killing bacteria should probably take priority [4].

Our genetic study will look at a panel of genes. Of particular interest, we are going to include analysis of the CysGlyGln haplotype of the ADRB2 (b2-adrenergic receptor) gene associated with a markedly worse survival in sepsis and also analysis of the proprotein convertase subtilisin/kexin type 9 (PCSK9) as the AA-genotype is associated with a significantly increased risk of death in sepsis.

References

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2) de Coupade C, Gear RW, Dazin PF, Sroussi HY, Green PG, Levine JD. Beta 2-adrenergic receptor regulation of human neutrophil function is sexually dimorphic. Br J Pharmacol. 2004 Dec;143(8):1033-41.
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4) Pemberton P, Veenith T, Snelson C, Whitehouse T. Is It Time to Beta Block the Septic Patient? Biomed Res Int. 2015;2015:424308. doi: 10.1155/2015/424308. Epub 2015 Oct 18.