ELECTIVE (SSC5a) REPORT (1200 words)

A report that addresses the above four objectives should be written below. Your Elective supervisor will assess this.

My interest in amyloid began during my undergraduate degree at the University of Leeds where I completed a literature review on amyloidosis, under my supervisor who manages an amyloid laboratory research group. In my Masters degree, I joined this same amyloid research team to undertake a project using an in vivo beta-lactamase assay to analyse the sequence-structure relationship responsible for systemic (AL) amyloidosis. Throughout medical school my interest in both research and amyloidosis have continued, but I felt that I have had little experience in the two over the past four years. My previous experience of researching the biochemistry of protein misfolding and amyloid has been the centre of my clinical interest with amyloidosis and I felt my elective placement would be the perfect opportunity to explore this interest further.

Describe the pattern of amyloidosis in the UK population

Amyloidosis is an umbrella term for a number of conditions which are characterised by a pathological process whereby proteins misfold into a toxic amyloid protein. The amyloid may accumulate and deposits in various tissues (e.g., cardiac, renal and hepatic tissue) which may lead to organ dysfunction. Amyloidosis can be classified into systemic and localised, based on the distribution of amyloid deposits in the body. Additionally, the subclass of amyloidosis is named after the type of protein which is forming amyloid to cause a certain medical condition. Examples of systemic amyloidosis include light chain (AL), wild-type TTR, hereditary TTR and AA amyloidosis (1) (2). In contrast, localised amyloidosis may affect different sites and although it does not transition into widespread amyloid deposition, the local accumulation of amyloid fibrils can still cause significant clinical disease.

In 2013 Pinney et al., published a large epidemiological study describing the pattern of systemic amyloidosis in the United Kingdom during 2008. Overall, the data estimates an annual incidence of 0.8/100,000 for systemic amyloidosis, with AL amyloidosis being the most common form (3). Additionally, the incidence of amyloidosis increased with age, peaking between ages 60-79 years. Interestingly, the team found the prevalence of amyloidosis doubled over the course of the study, suggesting this is likely due to a combination of improved diagnostics and increasing awareness of this rare medical condition.

Describe the pattern of health provision for amyloidosis in the UK

The National Amyloidosis Centre (NAC) is the only centre in the UK which centres on the diagnosis and medical management of patients with amyloidosis. Initially, patients are referred to the NAC by their local hospitals. Patients will visit the NAC for an individual assessment over 1-2 days, including an overnight stay in local accommodation. The specialised facilities at the NAC allow a thorough and efficient clinical assessment for each patient including: baseline blood tested, an echocardiogram, a nuclear medicine SAP scan, followed by a physician-led consultation with the results from the named tests. The clinician is able to analyse and quantify the amyloid deposition in the body and request additional diagnostic tests if necessary, such as a DPD nuclear scan, cardiac MRI or genetic testing. If treatment is required, patients will initially be counselled about the type of treatment at the NAC (1). But fortunately, the majority of treatment regimens can be completed with the patient's local hospital under the advice of the NAC. To monitor for disease progression, patients with amyloidosis undergo long-term surveillance both locally and with the NAC. Patients usually visit the centre at The Royal Free Hospital annually whereby they undergo the same 48-hour process and receive a clinical review with their physician. In the interim, the centre organises for their patients to have regular blood tests which are sent to the NAC on a regular basis to monitor the trend of their condition.

Clearly, the NAC provides health care to the highest standard for patients with amyloidosis. In terms of health provision, all NHS-patients can utilise this service for free at the point of care.

To describe the treatment options for AL amyloidosis

The options for managing patients with AL amyloidosis hugely evolved over the past 20 years. Unfortunately, AL amyloidosis is currently incurable. However, the developed treatment regimens have the potential to control the disease process, reduce symptoms and overall improve a patient's quality of life. The management of AL amyloidosis

focuses on two key areas: 1) controlling and preventing the formation of new light-chain amyloid deposits and 2) supportive treatment options to controls symptoms and prevent future complications. The choice of treatment regimen is discussed and individualised for each patient based on their age, medical background, site and amount of amyloid deposition and lastly, the patient's preference (4).

In short, the treatment regimens can be classified into three branches: 1) initial treatment, 2) intensive initial treatment and 3) treatment of refractory and/or relapsed AL amyloidosis. The initial treatment aims to control the disease process by targeting and destroying the abnormal plasma cell population. Examples of treatment regimens that may be utilised include chemotherapy agents (e.g. cyclophosphamide and melphalan), steroids (e.g. dexamethasone and prednisolone), proteasome inhibitors (e.g. bortezomib), immunomodulatory drugs (e.g. thalidomide) and lastly, monoclonal antibodies (e.g. daratumumab). Often, clinicians may combine the mentioned agents to enhance the clearance of the abnormal plasma cells through different mechanisms. In the UK, the most common initial treatment regimen for AL amyloidosis is a combination of cyclophosphamide, bortezomib and dexamethasone, known as CVd. A small proportion of patients with AL amyloidosis who are deemed to be fitter and/or younger, may be advised to undergo a form of intensive initial treatment – known as high dose therapy with stem cell transplantation (HDT-SCT). HDT-SCT allows a high dose of chemotherapy to be administered, increasing the clearance of the abnormal plasma cell population. Usually, this would run the risk of also destroying the normal blood cell population which poses life threatening complications for the patient. HDT-SCT combines the high dose chemotherapy with an autologous stem cell transplantation to essentially saves the patient's blood cell population. Currently, as there is no cure for AL amyloidosis, patients are likely to relapse in the future following further accumulation and deposition of toxic amyloid fibrils at different organ sites. Again, there are a wide range of treatment options available and this may involve a repeat of the initial treatment. Alongside treatment, supportive measures are available to alleviate symptoms and aim to further improve the patient's quality of life (4).

To explore the day-to-day practice of doctors which are involved in both research and clinical practice

I initially decided to organise my elective placement at the National Amyloid Centre to further explore the possibility of participating in academic research alongside clinical work in the future. The NAC is a world-famous specialised site for both its academic research and medical care for patients with amyloidosis. The majority of research I have observed has been linked to clinical research trials whereby the healthcare team have discussed the eligibility of patients for particular trials (5).

I had the opportunity to discuss some ongoing work by Dr Joshua Bomsztyk and other team members. They have previously followed a cohort of 27 patients at the National Amyloidosis Centre with IgM-AL amyloidosis. Their study analysed their response to treatment with rituximab-bendamustine,and compared this to other chemotherapy regimens used previously (5). During my elective placement, Dr Bomsztyk has discussed the potential for myself to become involved in their follow-up analysis where they would like to assess whether the same cohort of patients have relapsed and if so, what form of treatment they have received since. We are hopeful this abstract may be submitted to the Internal Workshop for Waldenstrom's Macroglobulinaemia.

References

1. National Amyloidosis Centre. Amyloidosis Overview | Centre for Amyloidosis and Acute Phase Proteins - UCL – University College London [Internet]. Available from: https://www.ucl.ac.uk/amyloidosis/national-amyloidosis-centre/amyloidosis-overview#Amyloidosis
2. Amyloidosis - NORD (National Organization for Rare Disorders) [Internet]. Available from: https://rarediseases.org/rare-diseases/amyloidosis/
3. Pinney JH, Smith CJ, Taube JB, Lachmann HJ, Venner CP, Gibbs SDJ, et al. Systemic Amyloidosis in England: an epidemiological study. Br J Haematol [Internet]. 2013 May 1;161(4):525–32. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12286
4. AL amyloidosis: Your Essential Guide - AL amyloidosis Infoguide.
5. Manwani R, Sachchithanantham S, Mahmood S, Foard D, Sharpley F, Rezk T, et al. Treatment of IgM-associated immunoglobulin light-chain amyloidosis with rituximab-bendamustine. Blood. 2018 Aug 16;132(7):761–4.