Extended follow up of home therapy with hyaluronidase-facilitated subcutaneous immunoglobulin (fSCIg)

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Objectives

- Case review
  - Highlight a clinical dilemma
  - Steps taken in resolving the dilemma
  - Outcome and conclusions

- Present a **brand new** method of immunoglobulin replacement therapy.
Clinical History

- 28 year old caucasian woman.
- Presented in 2003 with severe asthma and recurrent chest and sinus infections
- 2005 developed neurological symptoms; 
  - muscle weakness
  - tremor

probable diagnosis......mitochondrial myopathy.
Background

- Prior to her neurological symptoms was **independent**.

- Since 2005 the **neurological symptoms** have **progressed**
  - requires a wheelchair
  - difficulty in swallowing
  - hearing and sight loss
  - slurred speech

- Symptoms have made it **difficult to continue independence living alone**; now lives with her parents.

- Has become increasingly **dependent on family**.
Laboratory Investigations

- IgG = 1.99 g/l  (6 – 16 g/l)
- IgA = 0.39 g/l  (0.9 – 3.4 g/l)
- IgM = 0.9 g/l  (0.48 – 1.9 g/l)

- Normal numbers of T-cell, B-cell and NK-cells
- Normal serum complement values
- Unresponsive to vaccinations
Diagnosis

Following the clinical history and laboratory tests was diagnosed with ............... 

primary antibody deficiency
Treatment

- Commenced on Ig replacement therapy initially intravenously.

- Once stabilised on treatment was given training for home therapy.

  Chosen route of administration was subcutaneous.
Treatment

- Inadequate trough IgG levels were being achieved.

- Dose of immunoglobulin was gradually **increased** until **maximal dose** was reached.....

  16g (100mls) infused over 4 sites weekly.

However was still **not achieving a therapeutic IgG level**; which varied from **2.32 – 5.66g/l**
Why?

The possible explanations:

1. Lack of compliance with administration of Ig replacement therapy

2. Increased immunoglobulin catabolism or

1. Increased immunoglobulin loss.
Investigation into the cause

- **No protein** in the urine
- **alpha1 anti-trypsin levels** in stool were normal
- **neonatal Fc receptor (FcRn)** sequencing did not identify a mutation.

- Time course study was performed
  - 20g Ig infused intravenously
  - **Series of blood samples** were taken to measure IgG level.
Results

- compliance with therapy was confirmed

- This demonstrates a significantly reduced half life of IgG at 8 days (normal 17-21 days) suggesting......

  hyper-catabolism
The patient was very disheartened and wanted to give up her treatment.

“what is the point of doing the infusions if it is not working?”

An alternative treatment regime needed to be explored.
Home therapy

- Patient’s strong preference was to continue treatment at home:
  
  To maintain **independence**
  To **reduce** hospital visits
  To maintain **control** of own treatment
  Reduce risk of **infection**
Treatment Options.....IVIg

- Two treatment methods; IVIg and SCIg replacement therapy

- **IVIg**
  - **poor venous access** and **tremor**; self cannulation – not possible
  - **family members** – not appropriate
  - Experiences **rate related reactions**
  - **Indwelling venous access devices** have the potential to cause additional complications.....**thrombotic and infectious risks**.

  Therefore **not an option for self administration at home**.

  - **Hospital infusions** – Quality of life
Treatment Options…..SClG (↑dose)

- Potential drawback is the **limited volume** that can be administered to a **single** site….
  - already receiving a **maximal dose per site** using 4 sites.
  - Increasing the Ig dose would result in;
    - **more frequent infusions**
    - more needles
    - dedicate more time for treatment

and **ultimately impact on the patients quality of life**.

However this treatment option would allow the patient to continue **self administration at home**.
New concept
Alternative Treatment Option.....fSCIg

- Novel treatment

Administering hyaluronidase prior to commencing SCIg....

Hyaluronidase facilitated subcutaneous immunoglobulin therapy (fSCIg)

- Allows a greater volume of fluid to be infused subcutaneously per site.
Hyaluronidase

- What is hyaluronidase?

It is a spreading or diffusing enzyme that temporarily increases the permeability of connective tissue through the hydrolysis of hyaluronan promoting diffusion of injected fluids or of localised transudates or exudates.

- Uses of hyaluronidase

To facilitate local anesthetics, opiate, antibiotic, insulin, fluid delivery and used to treat acute extravasation injury.
Two studies

- fSCIG ……using an intravenous product

- monthly doses of 25.5 to 61.2g (255 to 612 ml) can be infused into a single site, at rates of 120 to 300 ml/hr.\(^1,2\)

On discussion with the patient and gaining consent it was decided to use hyaluronidase to increase the volume of Ig infused per site to achieve therapeutic IgG level.


Treatment Plan

- **Skin test for hypersensitivity** to hyaluronidase was negative.

- **Control test** was performed;
  - **Comparison** between SCIg and fSCIg administering the current dose, 4g (25ml) of immunoglobulin.

  - results……..
Hyaluronidase Facilitated Subcutaneous Immunoglobulin Therapy (fSCIg)

Comparison between SCIg and fSCIg

Start of the infusion

During the infusion

End of the infusion
Developing the therapeutic regime

- Each week the dose of IgG was increased until desired trough IgG levels were achieved.

- **Dose of Ig**
  - increased from 4g (25ml) to 32g (200ml) delivered to one site.

- **Rate of the infusion**
  - increased from 14ml/hr to 120ml/hr.

- **Dose of hyaluronidase**
  - decreased from 150U/g of IgG to 50U/g of IgG.

- **Revised home therapy training**
  - Syringe drivers used in the community maximum rate 50ml/hr…average time taken from set-up, preparing the infusion and the infusion; 3hrs
Ig levels during SCIg and fSCIg

*Immunoglobulin Levels During SCIg and Following the introduction of Hyaluronidase Facilitated SCIg*
fSC Ig Infusion

Therapeutic IgG levels achieved with 20.8g (130ml) Ig per week

Before fSC Ig infusion.

End of infusion; 20.8g (130mls) infused at 100mls/hr.
Adverse effects

Adverse effects are minimal and occur both with SCIg and fSCIg

- Slight erythema
- Swelling
- No greater reaction than that seen with regular SCIg dose.
- No abnormalities of the infusion sites have been detected following 35 infusions over 12 months.
Summary

- Currently receiving 20.8g (130ml) of IgG to one site.

- Patient has elected to use two sites (both thighs) fortnightly.... 41.6g every two weeks

- Established and maintained therapeutic IgG level on this treatment regime......most recent IgG trough level being 9.31g/l
Conclusion

- Achieved therapeutic IgG levels……reducing potential risk to infections.

- fSCIG has permitted:
  - increase in IgG dose from **64g to 83.6g per month**, 
  - delivered in **4 rather than 16** subcutaneous infusions.

- Maintained the patients quality of life with self administration at home.

- **appears to be well tolerated**
  - experience is **limited** and long term safety studies are needed, together with quality of life and pharmacoeconomic assessments.
Follow-up

- Following **35 infusions** over **12 months**

  - Continues to self administer her treatment at home

  - Continues to maintain a **therapeutic IgG trough level**. The most recent level being **8.09 g/l**

  - Side effects are minimal

  - Skin – no abnormalities;
    - however slight change in **skin sensitivity** – feels **slightly numb** following completion of the infusion; resolves when the swelling has gone.
      - **unsure whether this is a new or not.**
Final thoughts

- Potential to revolutionise SC Ig replacement therapy administration.

- Also has wider implications for the administration of high dose.
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