

# Clinical and laboratory observation on immunoglobulin replacement therapy switching from an intravenous to a subcutaneous route in a Malaysian X-linked agammaglobulinemia patient

Adli Ali, DPhil(Oxon)<sup>1</sup>, Asrul Abdul Wahab, MPath(UKM)<sup>2</sup>, Amir Hamzah Abdul Latiff, MRCP(Ire)<sup>3</sup>, Intan Hakimah Ismail, PhD(Melbourne)<sup>4</sup>, Faizah Mohd Zaki, MMed(UKM)<sup>5</sup>, Boekhren Karyostyko Borhanuddin, MMed(UKM)<sup>6</sup>, Lokman Mohd Noh, FRCPE<sup>7</sup>

<sup>1</sup>Department of Paediatrics, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, <sup>2</sup>Department of Medical Microbiology & Immunology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, <sup>3</sup>Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia, <sup>4</sup>Department of Paediatrics, Faculty of Medicine and Health Science, University Putra Malaysia, Serdang, Malaysia, <sup>5</sup>Department of Radiology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Cheras, Kuala Lumpur, Malaysia, <sup>6</sup>National Heart Institute, Kuala Lumpur, Malaysia, <sup>7</sup>Tunku Azizah Hospital for Women & Children Kuala Lumpur

## SUMMARY

We report a clinical and laboratory observation in a boy with X-linked agammaglobulinemia (XLA) who underwent an immunoglobulin replacement therapy (IRT) via the subcutaneous route (IGSC) seven years after his IRT via intravenous route (IGIV). He was free of invasive infections when on IGIV but not the troublesome coughs a week before the next infusion. A switch to a subcutaneous route resulted in significant improvement of symptoms with good weight gain. When on 2-weekly IGSC cycle, adjusting dose for weight resulted in an IgG trough level of > 600 mg/dl.

## INTRODUCTION

Immunoglobulin replacement therapy (IRT) is mandatory for primary antibody deficiency to prevent infection.<sup>1</sup> The IRT has been administered via intravenous route until the 1990's after which the subcutaneous (SC) route became an optional route for children and adults.<sup>2</sup> Among the advantages of IGSC (immunoglobulin administered via subcutaneous route) are: a) obviate the need of intravenous route for difficult venous access; b) achieve stable serum IgG level instead of initial peak and lower trough level associated with IGIV (immunoglobulin administered via intravenous route) cycles; c) fewer systemic side effect than IGIV route; and d) more amenable towards home therapy for patients.<sup>3,4</sup> A common complication is a temporary subcutaneous tissue swelling at site of SC administration.

## CASE REPORT

A 12-year-old boy was diagnosed as X Linked Agammaglobulinemia (XLA) at the age of 4.5 years old. He began to have yearly episodes of pneumonia from the age of 1 year until 4.5 years at which time he suffered a lung empyema. Laboratory investigations showed the following: low serum immunoglobulins (mg/dL) IgG: 30 (504-1474),

IgA: 5 (27-195), IgM: 5 (15-259). The lymphocytes subsets count (cells/ $\mu$ L) were: CD19 (B cells) 9 (normal range: 500-1200), CD3(T cells) 7756 (1500-2900). A genetic study revealed a missense mutation at BTK gene loci with A>T substitution in exon 18 at nucleotide position 2020 of X-chromosome, confirming a diagnosis of X Linked Agammaglobulinemia.

He required IGIV since age of 4.75 years on a 4-weekly cycle. His episodes of pneumonia became less often until it stopped at the age of 6 years old. However, he continued to be unwell with wet coughs towards the end of each IRT cycle when trough serum IgG level depreciated to <400mg/dL; the 4 weekly cycle was reduced to 3 weeklies, increasing Immunoglobulin dose from 400 mg/kg to 500 mg/kg resulting in a trough serum levels IgG of > 500 mg/dL. Despite the dose increment (500mg/kg) he remained unwell with continuing episodes of coughs and a further episode of gastroenteritis including an adverse event while on IGIV administration. With an ongoing difficulty of venous access, a switch to an IGSC was inevitable.

His initial starting dose on IGSC was 7.5 gram of immunoglobulin weekly which was a bioequivalent of 5 grams intravenous weekly with washout period of 6 months, with dose adjustments to avoid excessive high serum IgG level. Once the patient maintained a stable serum IgG pre -infusion trough level of 600 mg to 1000 mg /dL on weekly IGSC, it was opportune to convert to longer 2-weekly subcutaneous dosing. The mean trough serum IgG level has been well above 600mg/L for the IGSC phase. The average IgG trough for each immunoglobulin dose level was 950-1080 mg/dL on weekly IGSC reducing to 600-800 mg/dL on 2-weekly IGSC cycle adjusted immunoglobulin dose with weight increment (Fig 1). While on IGIV average weight increased of 1.6 kg yearly was observed increasing to 3.5 kg yearly on IGSC. He was free of respiratory symptoms, a

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*Corresponding Author: Lokman M Noh*

*Email: lokman.m.noh@gmail.com*

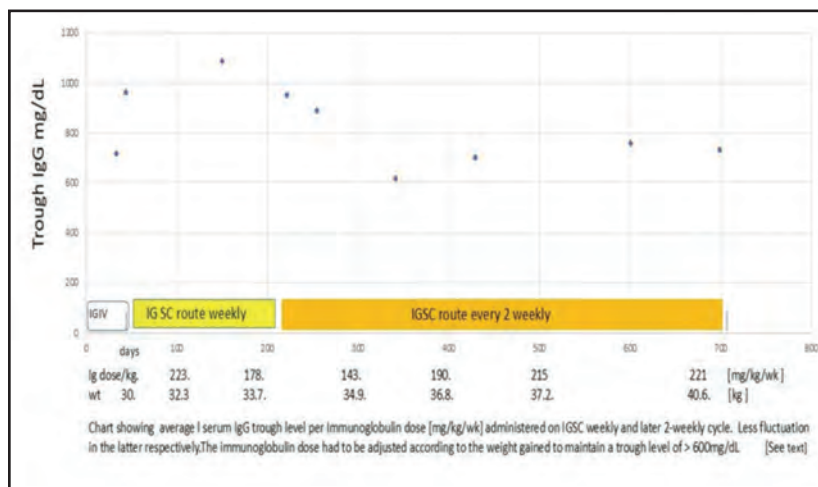


Fig. 1: Mean IgG trough levels for doses of immunoglobulin in an IRT switch from intravenous to subcutaneous in an XLA child.

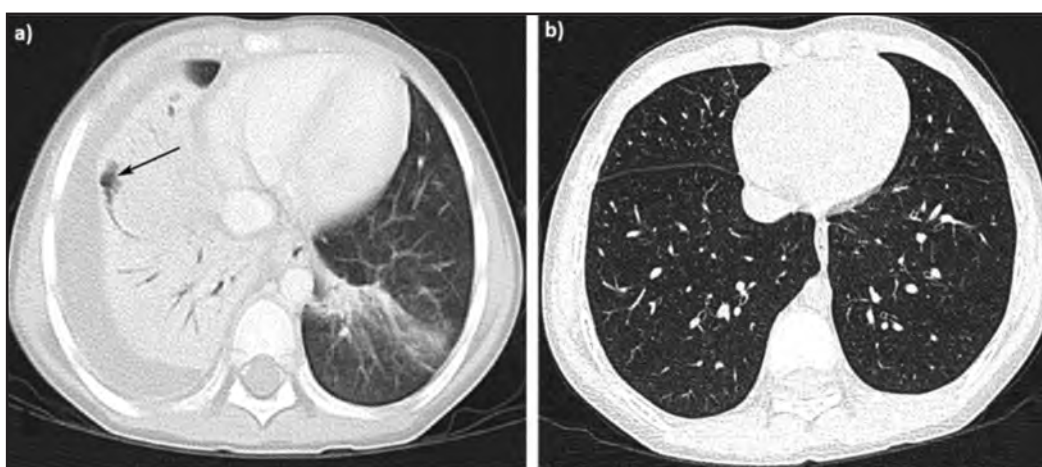


Fig. 2: CT-scan of the thorax at a) age of 5 years shows a collapsed consolidation with pleural effusion of the right lower lobe with a focal bronchiectatic changes at the periphery (black arrow), b) 3 months after the start of subcutaneous immunoglobulin therapy shows complete resolution of the consolidation, bronchiectasis and pleural effusion. The lung parenchyma is normal.

positive sense of well-being with no recorded adverse event while on IGSC.

The patient was noted to have bronchiectasis on chest CT-Scan imaging at age of 5 years, 3 months after IGIV commencement (Fig 2a). He had frequent upper respiratory infections cough at the end of each IRT cycle persisting even after dose modification reaching a trough IgG level above 500mg/dL. However, after commencement of IGSC weekly for 3 months, his repeated CT-Scan imaging showed resolution of bronchiectasis (Fig 2b). Although, this change could not be solely attributed to IGSC as no CT-Scan was done immediately prior to IGSC, it is conceivable that IGSC facilitate its resolution further, having been free of symptoms.

**DISCUSSION**

IGSC as a replacement therapy is a safe and efficacious to prevent serious bacterial infections while maximising patient satisfaction and quality of life.<sup>5,6</sup> Among the advantages of IGSC over IGIV are the fewer associated systemic effects

especially anaphylactic reaction that may occur with IGIV, however, the risk is reduced when converted to IGSC.<sup>5</sup> The first Scandinavian study with 33,000 SC infusions in 1995 recorded no anaphylactoid reaction.<sup>5,6</sup>

A trough IgG level of > 500mg /dL for both IGSC & IGIV to sufficient to prevent recurring infections in antibody deficiencies.<sup>3,7</sup> Titrating the dose towards a higher IgG trough level up to 960mg/dL progressively reduces the rate of infections beyond which it will not have further benefit.<sup>8</sup> To reduce the progression of bronchiectasis in XLA and CVID a trough level of > 500mg/dL is recommended, while a higher level of 800mg/dL is shown to prevent pulmonary changes.<sup>3,9</sup> Indeed our patient when on IGSC showed reduction in infections and complications, with resolution of bronchiectasis and good weight gain. This is highly remarkable as reports of improvement of bronchiectasis on IGIV is scarce although there was one report of changes on HRCT in more than 50% of patients receiving high dose intravenous immunoglobulin of 600-800 mg/kg/month with trough IgG levels of ≥600mg/dL.<sup>4</sup>

IGSC leads to a higher serum IgG with less fluctuating levels overall. With IGIV, the immunoglobulin is introduced directly into the veins, which will be redistributed in the intravascular and interstitial space. This leads to a high peak level in the early phase but with a heightened IgG catabolism, the level is decreased towards the end of the cycle, with an average half-life of 21-28 days. In comparison, IGSC administered weekly or biweekly resulted in the accumulation of IgG in subcutaneous tissue with a slower absorption into the circulatory system over 2-3 days producing a less fluctuating and a higher and stable serum IgG trough levels.<sup>10</sup> Every attempt should be made to switch to IGSC when venous access becomes difficult, obviating a need for the use of a fixed implantable venous device, a perpetual source of extraneous infections.

#### CONFLICT OF INTEREST

Nil as declared by the authors.

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