

# Low-dose subcutaneous alemtuzumab is a safe and effective treatment for chronic acquired pure red cell aplasia

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Three patients with pure red cell aplasia, with or without co-existing large granular lymphocytic leukaemia, who remained transfusion-dependent despite treatment with established first-line therapy, were treated with low-dose subcutaneous alemtuzumab 15 mg twice to thrice per week, for 3 to 4 weeks. The mean response time was 17 days compared with a response time of at least 61 days on standard first-line therapy. There were no serious side-effects and the mean duration of remission was 13 months. Low-dose subcutaneous alemtuzumab is a safe and effective treatment for pure red cell aplasia and further trials should be conducted to compare the long-term effectiveness of this treatment with conventional therapy.

## Introduction

Pure red cell aplasia (PRCA) is characterised by a severe normocytic anaemia and reticulocytopenia ( $<10 \times 10^9/L$ ), in which the bone marrow is normal except for a marked decrease or absence of erythroblasts. The disorder is classified into either congenital or acquired forms. Acquired acute cases are due to viral infections or drug-induced. By contrast, acquired chronic cases can be idiopathic or due to autoimmune disease (eg rheumatoid arthritis) associated with thymomas or lymphoproliferative disorders (especially large granular lymphocyte [LGL] leukaemia). A rare association has been found with patients on recombinant erythropoietin for chronic renal failure, in whom autoantibodies can develop against erythropoietin.<sup>1</sup>

Acquired chronic PRCA is typically treated as an immunologically mediated disease and several reports implicate T lymphocytes in its pathogenesis.<sup>2,3</sup> Corticosteroids constitute the treatment of choice, particularly in the absence of associated disease.<sup>4</sup> Other immunosuppressive therapies—namely cyclosporine, cyclophosphamide, antithymocyte globulin, plasmapheresis, and splenectomy—have also been shown to induce remission in some patients.<sup>5</sup> Treatment with alemtuzumab was first reported by Marsh and Gorden-Smith.<sup>6</sup>

Alemtuzumab (MabCampath; Genzyme, Sanofi-Aventis, US) is a monoclonal antibody that binds to the surface antigen CD52 and was initially developed for the prevention of graft rejection in kidney transplantation<sup>7</sup> as well as graft rejection and graft-versus-host disease in stem cell transplantation.<sup>8</sup> It is also used for the treatment of chronic lymphocytic leukaemia and T-cell lymphomas, as well as other immune-mediated disorders including arthritides, multiple sclerosis, vasculitis, and autoimmune cytopenias.<sup>9</sup> It causes depletion of T and B lymphocytes, and a single dose of alemtuzumab leads to rapid and profound lymphopenia. ‘First-dose’ transfusion reactions can be avoided by giving the drug subcutaneously without any loss of efficacy.<sup>10</sup>

### Key words

Immunosuppressive agents; Leukemia, large granular lymphocytic; Red-cell aplasia, pure

*Hong Kong Med J* 2013;19:549-52  
DOI: 10.12809/hkmj133798

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## Case reports

We report here the treatment of three patients—one with idiopathic PRCA and two of PRCA associated with LGL leukaemia. All of them were treated with low-dose alemtuzumab, 15 mg subcutaneously twice to thrice weekly for 3 to 4 weeks (total dose, 90-180 mg). The patients received paracetamol 500 mg as premedication. Local injection site redness was mild. Anti-infection prophylaxis was not used. Blood cytomegalovirus (CMV) antigen was monitored weekly for 6 weeks. Complete blood counts and absolute reticulocyte counts were monitored twice weekly until the disease responded.

### Case 1: idiopathic pure red cell aplasia

This 60-year-old man was first treated with prednisolone and cyclosporine for PRCA in

## 低劑量皮下注射阿倫單抗 (alemtuzumab) 治療慢性單紅血球再生不良症是一個安全及有效的方法

本文報告三名單紅血球再生不良 (PRCA) 患者，他們部份有大顆粒淋巴細胞白血病。患者用一線治療方案不成功後，再用阿倫單抗 (alemtuzumab) 15毫克進行皮下注射，每星期兩至三次，維期三至四星期。患者平均復元時間為17天，短於一線治療所需的61天。治療無嚴重副作用，平均康復時間為13個月。應用低劑量皮下注射 alemtuzumab 是安全及有效的治療，而其長遠的效果須與一線治療方案直接比試。

1993. He went into remission after 5 months, but the treatment was complicated by pneumocystis pneumonia and a perforated peptic ulcer. Cyclosporine was stopped and he remained in remission for 3 years. In June 1996, he suffered a relapse and was restarted on cyclosporine. After 5 months his haemoglobin (Hb) level returned to normal and this next remission lasted 126 months, although the cyclosporine was stopped after 1 year. His third relapse (with a Hb of 66 g/L, reticulocyte of  $13 \times 10^9$  /L, and marrow showing marked erythroblast depression) occurred in March 2007. This time he received alemtuzumab 15 mg subcutaneously 3 times a week for 4 weeks. His Hb level increased to 101 g/L after 13 days and his absolute reticulocyte count rose from  $13 \times 10^9$  /L to  $280 \times 10^9$  /L within 17 days. He has remained in remission up to the date of reporting (>40 months).

### Case 2: pure red cell aplasia associated with large granular lymphocyte

This 77-year-old man first presented in September 2001 with anaemia (61 g/L), LGL cells of  $1 \times 10^9$  /L and his marrow showed PRCA together with 20% LGL cells (CD3<sup>+</sup>, CD8<sup>+</sup>, CD56<sup>-</sup>, TCRαβ heterodimer<sup>+</sup>). He was treated with cyclosporine, low-dose prednisolone, and erythropoietin with a partial response; his Hb fluctuated between 85 and 110 g/L. Cyclosporine was discontinued after 5 years due to renal toxicity. One year later, his Hb had decreased to 75 g/L; he had reticulocytopenia ( $8 \times 10^9$  /L) but no LGL cells were evident in his blood. In January 2007, he was treated with low-dose alemtuzumab. On day 18, the absolute reticulocyte count had increased from  $8 \times 10^9$  /L to  $166 \times 10^9$  /L. He remained in remission for 15 months, and suffered a second relapse of anaemia, which was again treated with low-dose alemtuzumab. His Hb increased from 72 to 100 g/L. There was a slower change in the absolute reticulocyte count from 7 to  $40 \times 10^9$  /L after 38 days and  $94 \times 10^9$  /L after 65 days. In this second remission, he remained transfusion-independent for over 10 months.

### Case 3: pure red cell aplasia associated with large granular lymphocyte

This 71-year-old man first presented with lymphocytosis ( $4.57 \times 10^9$  /L with 61% LGL cells which were CD3<sup>+</sup>, CD8<sup>+</sup>, CD56<sup>-</sup>, TCRαβ heterodimer<sup>+</sup>) and started taking chlorambucil and prednisolone for LGL leukaemia in April 2002. The lymphocytosis remitted and the Hb rose from 107 to 120 g/L. The patient relapsed 4 years later with more severe anaemia (Hb, 89 g/L), with a reticulocyte count of  $36 \times 10^9$  /L (0.8%) and LGL cells (10%) in his blood. Repeat marrow biopsy showed PRCA and only three small lymphocyte aggregates. He had a minimal response to chlorambucil and erythropoietin, and was transfusion-dependent for the next 4 months. As the patient was not responding to treatment, he was started on alemtuzumab 15 mg twice per week for 4 weeks. His Hb was maintained at 120 g/L without recourse to further blood transfusions and by day 19 of treatment his reticulocyte count had also improved (from  $36 \times 10^9$  /L to  $168 \times 10^9$  /L; a 4-fold increase). During treatment, the patient suffered transient fever and CMV antigen was detected. He was therefore treated with intravenous ganciclovir for 1 week and valganciclovir orally for 3 weeks. His fever responded on day 2 and he remained well. Subsequent weekly testing for CMV antigen remained negative.

After being in remission for 7 months, he presented with a Hb level of 99 g/L, but with a reticulocytosis ( $224 \times 10^9$  /L). As his Coombs' test was positive, he was diagnosed as having autoimmune haemolytic anaemia. He responded poorly to prednisolone but promptly to a second course of alemtuzumab, and remained in remission for 27 months. A third relapse of anaemia occurred in August 2010. This time the Hb level was 75 g/L, the reticulocyte count was  $40 \times 10^9$  /L, the Coombs' test was positive 3+/4, and there were LGL cells (4%) in the blood. Marrow biopsy showed PRCA and no LGL infiltration. Once again he was treated with alemtuzumab with a good response. His reticulocyte count increased from 40 to 128 and  $199 \times 10^9$  /L by day 13 and 31, respectively. He remains in remission (>6 months).

## Discussion

These cases demonstrated a mean response time for patients treated with alemtuzumab of 17 days from the start of the injections (measured as an increase in absolute reticulocyte count  $>100 \times 10^9$  /L and Hb  $>100$  g/L). Only one of the three patients suffered treatment side-effects. Case 3 developed CMV viraemia, which manifested as fever and was effectively treated with ganciclovir. The mean duration of remissions (when the patient was transfusion-independent) was 13 months (range, 7 months to >40 months).

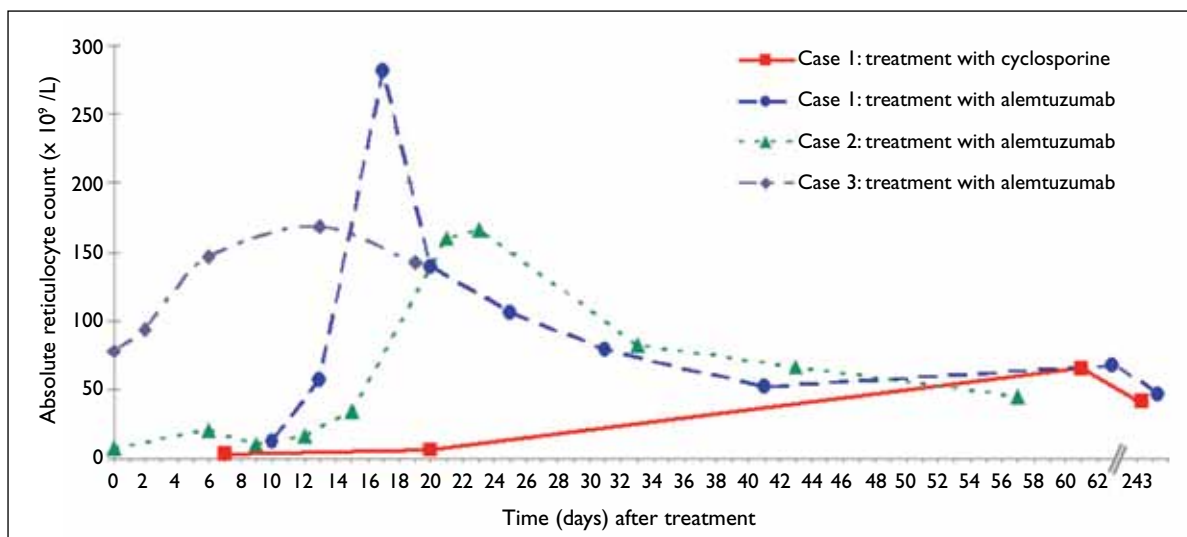


FIG. Changing absolute reticulocyte counts over time in relation to initiation of cyclosporine and alemtuzumab treatment for pure red cell aplasia

We can compare these data with more established treatment. In case 1, the patient initially received prednisolone and cyclosporine, but suffered from treatment complications (viz pneumocystis pneumonia and a perforated peptic ulcer). During his first remission, he was again treated with cyclosporine. It took 61 days to show an increase in the absolute reticulocyte count from  $3 \times 10^9 / L$  to  $65 \times 10^9 / L$  (Fig). In case 3, the patient was initially treated with chlorambucil as first-line therapy. The absolute reticulocyte count did not demonstrate any significant response for 4 months.

Idiopathic PRCA is an autoimmune disorder due to hyperactive T cells.<sup>2,3</sup> T-cell LGL is a clonal chronic lymphoproliferative disease that is frequently complicated by PRCA. According to our experience, both conditions responded promptly to alemtuzumab (a T-cell cytotoxic antibody), which suggests that the two disorders are a spectrum of the same disease. In fact, for patient 3 (with obvious LGL on presentation), when his anaemia relapsed for the third time, LGL cells accounted for only 4% of white cells in peripheral blood and were absent in the marrow. In both instances, he responded promptly to alemtuzumab.

Other reports of the treatment of PRCA with alemtuzumab have, generally, used higher doses (130 mg to 490 mg by Au et al<sup>11</sup> and 300 mg by Ru and Liebman<sup>12</sup>). We used a much smaller dose, namely 15

mg (about 10 mg/m<sup>2</sup>) subcutaneously, twice or thrice weekly for 3 to 4 weeks (total dose of 90-180 mg), and could still achieve a rapid and effective response.

Risitano et al<sup>13</sup> summarised the European group for Blood and Marrow Transplantation experience and reported on 12 PRCA patients treated with subcutaneous alemtuzumab (30 mg daily for a total of 300 mg), followed by cyclosporine maintenance. The response rate was 84% (8 complete remissions and 2 partial remissions); only three patients had CMV reactivation that subsequently responded to ganciclovir. Five patients relapsed but all responded upon re-treatment. We did not use cyclosporine maintenance, and yet the median response duration was 13 months. Two of the three patients relapsed, but responded promptly to retreatment.

Infection is an important complication of alemtuzumab. One study reported 56% of patients who developed opportunistic infection; herpesvirus infections were the most common, with CMV viraemia occurring in 44% of patients.<sup>14</sup> Other infections occurred in 82%, including upper respiratory tract infections, tuberculosis, sepsis and/or bacteraemia.<sup>14</sup> In our series, only one of three patients suffered a mild CMV viraemia that was treated effectively with ganciclovir. The low frequency of infections in these cases was probably due to the use of low-dose, short-duration alemtuzumab therapy.

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## Answers to CME Programme

### *Hong Kong Medical Journal* October 2013 issue

Hong Kong Med J 2013;19:386-92

**I. Tuberculin sensitivity testing and treatment of latent tuberculosis remains effective for tuberculosis control in human immunodeficiency virus-infected patients in Hong Kong**

- |   |          |          |          |         |         |
|---|----------|----------|----------|---------|---------|
| A | 1. True  | 2. False | 3. False | 4. True | 5. True |
| B | 1. False | 2. True  | 3. False | 4. True | 5. True |

Hong Kong Med J 2013;19:400-6

**II. Age, tumour stage, and preoperative serum albumin level are independent predictors of mortality after radical cystectomy for treatment of bladder cancer in Hong Kong Chinese**

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|---|----------|----------|----------|----------|----------|
| A | 1. True  | 2. True  | 3. False | 4. True  | 5. False |
| B | 1. False | 2. False | 3. True  | 4. False | 5. False |