Case report

Effects of high dose intravenous immunoglobulin in two severe corticosteroid insensitive asthmatic patients

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Abstract

Preliminary observations of the clinical efficacy of intravenous immunoglobulin in two patients with severe corticosteroid insensitive asthma are reported. In both patients treatment with intravenous immunoglobulin resulted in clinical improvement and enabled a significant reduction in the dose of prednisolone. In one of the patients fibreoptic bronchoscopy with endobronchial biopsies was performed and peripheral blood was analysed by flow cytometry before and after treatment. Immunohistological analysis of the biopsy samples after treatment showed a decrease in the number of all cell types, especially CD3+ T cells, CD4+ T cells, and activated CD25+ T lymphocytes, which was associated with a reduction in peripheral blood T cell activation. Intravenous immunoglobulin may be a valid option for the treatment of corticosteroid insensitive asthma. To elucidate the role and mode of action of intravenous immunoglobulin further studies in larger groups of patients are needed.

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The use of intravenous immunoglobulin (Ig) in the treatment of severe asthma was found to be beneficial in one open study of clinical efficacy.[1] We treated two severe asthmatic patients who were found to be corticosteroid insensitive as judged by requirements of high doses of systemic corticosteroids, low prebronchodilator forced expiratory volume in one second (FEV_1) values (<70%), and decreased sensitivity of peripheral blood mononuclear cells to the inhibitory effects of dexamethasone in vitro.[2] In one of the patients we have determined the effects of intravenous immunoglobulin treatment on T lymphocyte and eosinophil numbers and their state of activation in endobronchial biopsy specimens and peripheral blood. In the same patient we have investigated the ability of intravenous immunoglobulin to modulate the concentration of interleukin 8 (IL-8) and its IgG autoantibodies in the circulation.

Case reports

CASE 1

A 15 year old girl with corticosteroid insensitive asthma was admitted to our hospital. On admission she was dyspnoeic at rest with a Cushingoid appearance. Lung function tests showed an obstructive pattern (FEV_1 57%, forced vital capacity (FVC) 80%, airways resistance (Raw) 372% of predicted). Peak expiratory flow (PEF) variability was 65%. Total IgE was 2280 IU/l (normal <80 IU/l) with positive radio allergosorbent tests (RAST) for house dust mite and other aeroallergens.

Despite optimal treatment consisting of prednisolone (60 mg/day), inhaled budesonide (3000 µg/day), theophylline, and nebulised bronchodilators, her asthma proved difficult to control. Increasing the dose of oral prednisolone to 100 mg daily led to a modest decrease in PEF variability to 40%. Additional treatment with methotrexate did not result in clinical improvement or reduction of the dose of prednisolone, and was associated with considerable gastrointestinal side effects. After four weeks methotrexate was therefore discontinued (fig 1).

Treatment with intravenous immunoglobulin (Sandoglobulin, Sandoz, Bern, Switzerland) in a dosage of 84 g once a month (2 g/kg body weight) was commenced five months after admission. After two months of treatment there was a clear clinical improvement associated with a reduction in PEF variability to 10%, enabling the dose of prednisolone to be reduced to 10 mg/day. Mean morning PEF increased from 160 to 320 l/min, PEF variability decreased to 5%, and FEV_1 and FVC were 96% and 95% of predicted (fig 1).

CASE 2

The second patient, an 18 year old woman with a history of severe, poorly controlled asthma, was admitted to our institution in 1992 for evaluation and treatment. Since 1986 her asthma had been difficult to control with episodes of nocturnal symptoms and frequent emergency room visits. On admission we saw a dyspnoeic woman with Cushingoid features and FEV_1 of 51% predicted. Treatment consisted of prednisolone (30 mg/day), inhaled budesonide (2400 µg/day), formoterol, and nebulised bronchodilators. Increasing the dose of prednisolone to 90 mg/day did not lead to

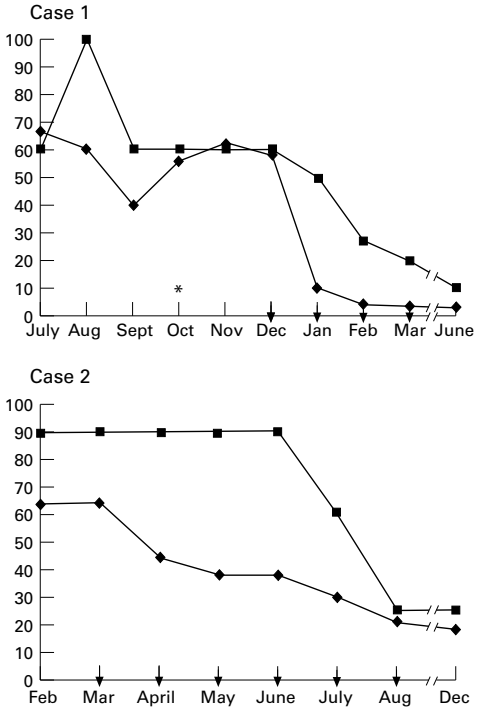

*Figure 1 Decrease in PEF variability (◆) and doses of prednisolone (■) in the two patients following treatment with intravenous immunoglobulin (▼). In case 1 * marks the introduction of methotrexate (15 mg/week).*

clinical improvement (FEV_1 58% of predicted).

In March 1993 intravenous immunoglobulin therapy (2 g/kg body weight/month) was introduced. Fibreoptic bronchoscopy with endobronchial biopsy samples and flow cytometric analyses of peripheral blood were performed before and after four months of treatment. During the period of treatment with intravenous immunoglobulin her medication was kept constant including oral prednisolone (90 mg/day) and inhaled budesonide (2400 µg/day). The mean asthma symptom score decreased from 8.9 to 5.1. PEF variability improved from 64.1% to 37.7%. Treatment with intravenous immunoglobulin was continued after the second bronchoscopy for a further two months during which oral prednisolone could be reduced from 90 to 25 mg/day while PEF variability improved further to 15% (fig 1). This was accompanied by an increase in FEV_1 from 68% of predicted before to 98% of predicted after six months of treatment. One year after intravenous immunoglobulin was introduced no exacerbations have occurred.

Immunohistological analysis of bronchial tissue after treatment with intravenous immunoglobulin revealed a decrease in the number of all cell types, especially CD3+ T cells, CD4+ T cells, and activated CD25+ T lymphocytes (table 1). Similarly, flow cytometric analysis of peripheral blood showed a decrease in CD3+ and CD4+ T cells bearing IL-2R and HLA-DR as well as reduced percentage of activated CD23+ B cells (table 1). Total serum IgE was decreased by 51% (from 3320 to 1622 IU/l) while IgG levels increased from 8.1 to 29.6 g/l (normal range 8–17 g/l). Free IL-8 was reduced by 72% (from 0.232 to 0.064 ng/ml), together with a 178% increase in IL-8/IgG complexes (from 0.061 to 0.170 units/ml) and a 28% increase in free IgG autoantibody (from 0.341 to 0.438 units/ml). Serum eosinophilic cationic protein (ECP), measured before and one week after the first infusion of intravenous immunoglobulin, showed a decrease from 34.6 µg/l (normal <16.0 µg/l) to undetectable levels and stayed undetectable throughout the remaining treatment period.

Table 1 Results of immunohistological analyses of bronchial biopsy specimens and flow cytometric analyses of peripheral blood before and after treatment with intravenous immunoglobulin in case 2

	Before	*After*	*% change*
Biopsy specimen*			
Leucocytes (CD45)	160	117	−27
T cells (CD3)	116	84	−28
T helper cells (CD4)	58	26	−55
T suppressor cells (CD8)	25	20	−20
Interleukin 2 receptor (CD25)	30	14	−53
Neutrophils (elastase)	25	18	−28
Mast cells (tryptase)	18	15	−17
Activated eosinophils (EG2)	8	6	−25
Blood			
Leucocytes ($\times 10^6$/ml)	5.6	5.6	0
Differential count			
Neutrophils (%)	50	57	12
Basophils (%)	0	0	0
Eosinophils (%)	9	8	−12
Monocytes (%)	8	6	−25
Lymphocytes (%)	33	25	−12
Flow cytometry of lymphocytes			
CD3 (%)	80	69	−14
CD4 (%)	39	36	−8
CD4/CD25 (%)†	7.1	1	−86
CD4/HLA-DR (%)†	5.9	1	−83
CD8 (%)	32	25	−22
CD8/CD25 (%)†	0.5	0	−100
CD8/HLA-DR (%)†	13.9	1	−92
CD19 (%)	3	7	133
CD19/CD23 (%)†	68	56	−18

*Number expressed as total cell count per mm^2 submucosa located beneath the basement membrane.
†Percentages of T and B lymphocytes expressing activation markers CD25 (IL-2R), HLA-DR (MHC class II), and CD23 (low affinity IgE receptor).

Discussion

In two patients with corticosteroid insensitive asthma treated with high doses of intravenous immunoglobulin we have observed a clear therapeutic benefit consisting of improved and long lasting control of asthma. This enabled a reduction in the dose of oral corticosteroids which in both patients was associated with significant morbidity. These observations are consistent with those of Mazer and Gelfand.[1]

In the second case the improvement in airway inflammation was associated with a reduction in markers of disease activity in peripheral blood. Among the immunomodulating capacities of intravenous immunoglobulin, its potential to suppress T cell activation and B cell differentiation into antibody-secreting cells is relevant to asthma.[3] Although the knowledge about the composition of intravenous immunoglobulin is incomplete and hence the action of the individual components unclear, soluble CD4, CD8, and HLA molecules have recently been detected in commercially available immunoglobulin preparations.[4] It is possible that intravenous immunoglobulin exerts a therapeutic effect via interaction between soluble CD4 and HLA class II molecules on antigen-presenting cells, resulting in non-

specific immunosuppression with decreased expression of IL-2R on T cells and subsequently reduced secretion of cytokines such as IL-4 and IL-5.

There is growing evidence that IL-8 plays an important role in the recruitment of inflammatory cells into the lungs of asthmatic subjects.[5] Intravenous immunoglobulin may contain autoantibodies against cytokines, such as anti-IL-8 autoantibody, which neutralise their biological effects.[6] The reduction in free IL-8 appears to result from its binding with the blocking IgG anti-IL-8 antibody present in intravenous immunoglobulin, a hypothesis that is supported by the substantial increase in IL-8/IgG complexes after treatment.

To clarify the role and mode of action of intravenous immunoglobulin in the treatment of corticosteroid insensitive asthma, further studies in larger groups of patients are needed.

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