

Letter to the Editor

Approved and unapproved use of immunoglobulins in Iceland

To the Editor:

Immunoglobulin therapy has been increasingly used in the treatment of various diseases for decades.¹⁻⁵ Congenital or acquired immunodeficiency, especially with prominent antibody deficiency or agammaglobulinemia, is a clear indication for treatment with undisputed results.^{2,5-7} This treatment has also been accepted in several autoimmune diseases as an immunomodulating therapy.^{1-3,8} The Icelandic Medicines Agency has approved the use of intravenous immunoglobulin in 8 disease processes, similar to the European Medicines Agency and the Food and Drug Administration. Because this treatment has proven effective in some autoimmune diseases, it has encouraged its use for the treatment of many other disorders¹⁻⁵; however, this use often lacks scientific foundation (unapproved, unlicensed, unregistered, off-label, or compassionate). The use of immunoglobulin treatment has so far been described in more than 150 different conditions, including neurologic diseases and autoimmune disorders,^{1-3,7} and unapproved use has in some countries exceeded the approved use.²

The aim of our study was to investigate the use of immunoglobulin therapy in Iceland with emphasis on the indications for treatment, in particular the approved and unapproved indications.

Data for immunoglobulin treatment for the years 2001 to 2009 were retrieved from hospital records and a pharmacy registry at Landspítali – University Hospital (indication for treatment, date, sex, age, and dosage). The hospital pharmacy has strict oversight over all immunoglobulin prescriptions in Iceland. For unapproved treatment, additional information is required and the physician must put forward arguments for the treatment including indication, aim, and assessment of the treatment. The indications were categorized according to the medical specialty of the doctor prescribing the treatment and also recorded whether the indication was approved or not.

The study was approved by the Hospital Ethical Committee (46/2009), the Data Protection Authorities in Iceland (2009/873), and the director of the hospital. Statistical calculations were done in SPSS, and statistical significance was set at P less than .05.

In the study period, 402 individuals received immunoglobulin treatment prescribed at the hospital. Intravenous immunoglobulin treatment was given to 389 patients, and of these, 296 were treated on an outpatient basis. Subcutaneous immunoglobulin therapy was given to 13 patients.

The median age of the patients was 53.8 years (8 months-90 years), 234 were females (58%), and 168 were males (42%), with the sex difference being significant ($P = .020$).

The indication for treatment was unclear in 28 patients; of the remaining individuals, approved indications were 264 (70.6%) and 110 were unapproved (29.4%). The sex difference in all patients was 234 women and 168 men ($P = .014$). For approved indications, the sex difference was 120 women and 144 men, the difference not being significant, but for unapproved indications, the sex difference was 73 women and 37 men ($P = .014$).

Indications for treatment are given in Table I. For immunologic diseases, the most common indications were immunodeficiency with predominantly antibody defects (57 patients, including hypogammaglobulinemia, selective deficiency of immunoglobulin

TABLE I. Indications for intravenous immunoglobulin treatment, categorized by disease classification

Disease classification	Number
Immunodeficiency	
Immunodeficiency with predominantly antibody defects	57
Immunodeficiency associated with other major defects	4
Common variable immunodeficiency	20
Other and unspecified immunodeficiencies	26
Other disorders involving the immune mechanism, not elsewhere classified	5
Unclear diagnosis	11
Other	5
Total	128
Cancer	
Acute lymphoblastic leukemia	8
Chronic lymphocytic leukemia	23
Non-Hodgkin's lymphoma	26
Multiple myeloma	33
Other	9
Total	99
Neurologic diseases	
Chronic inflammatory demyelinating polyneuropathy	17
Gullain-Barré syndrome	16
Multiple sclerosis	10
Myasthenia gravis	8
Postinfection fatigue syndrome	4
Other	11
Total	66
Hematologic diseases	
Idiopathic thrombocytopenic purpura	37
Kawasaki	11
Total	48
Rheumatologic diseases	
Systemic lupus erythematosus	16
Rheumatoid arthritis	2
Other	5
Total	23
Pulmonology diseases	
Asthma	12
Chronic obstructive pulmonary disease	6
Other	1
Total	19
Dermatology diseases	
Urticaria and atopic dermatitis	
Total	4
Other	
Total	15

subclasses, and antibody deficiency) and common variable immune deficiency (20 patients). For oncologic diseases, multiple myeloma (33 patients), chronic lymphocytic leukemia (23 patients) as well as intravenous immunoglobulin in connection with cancer treatment were the most common indications. For neurologic diseases, Gullain-Barré syndrome (16 patients) was the most common indication. For hematologic diseases, idiopathic thrombocytopenia (37 patients) and Kawasaki disease (11 patients) were the most common indications. For rheumatologic diseases, systemic lupus erythematosus (16 patients) was the most common indication.

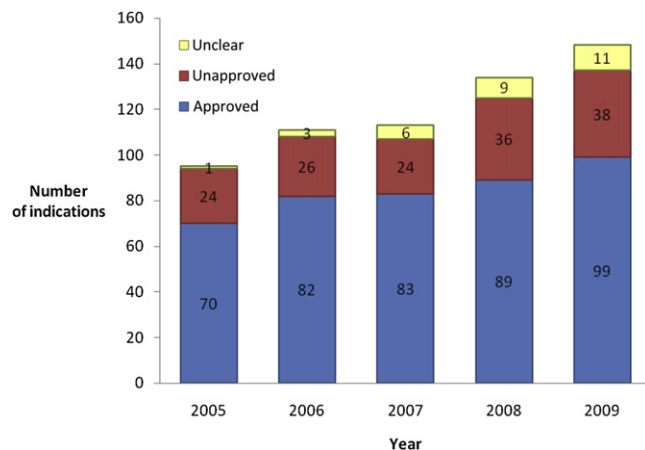


FIG 1. Comparison of approved, unapproved, and unclear indications for immunoglobulin therapy during the period 2005 to 2009.

The specialty of the prescribing physicians was most often immunology, hematology, and oncology. There were 94 (23%) children younger than 18 years.

The usage of immunoglobulins increased constantly during the period (Fig 1), the increase in women being more prominent than in men ($P = .011$). Approved indications were more common than unapproved indications throughout the study period.

During the study period, a continuous increase in immunoglobulin usage was observed. In our study, approved indications clearly exceeded the unapproved indications. This is noteworthy because in some neighboring countries the unapproved use is exceeding the approved ones.² Moreover, in our study, the increase in immunoglobulin usage was more prominent in the approved category, contradicting some other published studies.² This may reflect a cautious use of this treatment in Iceland, but it must also be kept in mind that this treatment may be beneficial to patients suffering from diseases without approved indication.^{1,2} The indications for immunoglobulin treatment were virtually unchanged during the study period except for a slight increase in connection with cancer treatment.

Immunodeficiency diseases were the most common indications, followed by hemato-oncology. These are all well-defined indications and in context with other Western countries.^{1-3,6,7}

Neurologic diseases form the third largest group in our study. This is of interest because except for Guillain-Barré syndrome in most countries, all neurologic disorders are unapproved indications.^{2,8} Therefore, the most common unapproved or compassionate use of immunoglobulins in our study was for neurologic diseases. This is similar to results of other studies.^{1-3,8} This is interesting because some of the neurologic diseases may have an autoimmune background.

Several other diseases are treated with immunoglobulins despite lack of scientific data, and this seems to be similar in our study as previously described.¹⁻³

Most of the children were treated for immune disorders or other approved indications. Our results seem to be in concordance with other reports.¹⁻³

Interestingly, more women than men received immunoglobulin therapy during the study period. This difference was largely related to more unapproved use in women. Although women have a higher incidence of many autoimmune diseases and neurologic disorders than do men, we do question whether this entirely explains this observed difference in the sex ratio. It is important to use immunoglobulin treatment cautiously but sensibly. Treatment with immunoglobulins is often very effective, but the cost can be high and must be taken into consideration. Unapproved use can certainly be accepted, but at the same time, the need for a better understanding of these diseases and the treatment is evident. It is hoped that research in the near future will facilitate this development.

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Bryndís Ester Ólafsdóttir, BSc^a

David Þór Þorsteinsson, MD^{b,c}

Rannveig Einarisdóttir, MSc^{c,d}

Björn Rúnar Lúðvíksson, MD, PhD^{c,e}

Gerður Gröndal, MD^{c,f}

Kristján Erlendsson, MD^{c,e}

Ásgeir Haraldsson, MD, PhD^{a,b,c}

From ^athe Faculty of Medicine, University of Iceland, ^bChildren's Hospital Iceland, ^cLandspítali – University Hospital, ^dthe Division of Pharmaceutical Affairs, and the Departments of ^eImmunology and ^fMedicine, Landspítali – University Hospital, Reykjavík, Iceland. E-mail: asgeir@lsh.is.

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