Clinical Dermatology 2000

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Satellite Symposium on High-dose Intravenous Immunoglobulin (HDIVIG) in Dermatology

Speaker: Dr. S. Jolles

IVIG has been tried in the treatment of a variety of skin diseases. Reports on use of IVIG in dermatology are largely confined to uncontrolled trials or case reports though there is a single controlled trial of IVIG as adjunctive therapy in dermatomyositis reported.

Now third generation products are available. They utilize several viral inactivation steps (for example, Cohn fraction, trace pepsin, solvent-detergent, pasteurisation and nanofiltration) with an excellent safety record.

Pemphigus Vulgaris

Speaker: Dr. D. Jullien

There is an circulating anti-demosglein-3 antibody, which binds to a 130 kDa glycoprotein causing subsequent acantholysis.

When high dose IVIG is used in pemphigus vulgaris, it is proposed to be used in **refractory** cases, as **adjunctive therapy** to second-line agents (for example, in poor responders and in cases with severe adverse effects) and when a **rapid disease control** is essential.

IVIG therapy has to be given in courses. Each course consists of using IVIG 0.3-0.4 g/kg/day for 3-5 days. One or more than 15 courses have been used. Interval between each cycle/course varies from 15 days to three months. A common usage is to give 0.4 g/kg/day for five days for three courses, with an interval of four weeks between each cycle. The tolerability is good. Side effects are usually mild (for example, headache, tachycardia etc). No serious side effects have been reported (based on the 21 case reports on literature so far). Following infusion, there is usually a sharp fall of the serum IgG autoantibodies, though relapse may occur.

Bullous Pemphigoid

Speaker: Dr. D. Jullien

In this disease, the antibody binds to BP180 Ag.

The therapy used 0.3-0.4 g/kg/day, for five days totally for 1-5 courses.

When used as a monotherapy, there could be no response or there was rapid but very transient response.

When used as an adjunctive therapy, there was rapid control of the disease, and steroid sparing effect could be obtained. It was not known whether longer remission could occur with repeated courses.

Therefore it is recommended that high dose IVIG should be used for bullous pemphigoid that are **unresponsive to conventional therapy**, as **adjuvent therapy** and when **a rapid disease control** is needed.

The author concluded that there was a greater need for controlled trials for use of high dose IVIG in pemphigus vulgaris than bullous pemphoid. The areas to be explored include its efficacy, dose and the interval between cycles, etc.

IVIG Therapy for Ocular Cicatricial Pemphigoid

Speaker: Dr. A. Razzzaque

Ten patients not responding to immunosuppressive treatment were chosen to receive IVIG.

Skin biopsy of the inflamed conjunctiva showed immunoglobulin and/or complement deposition at the

epithelial basement membrane zone in these patients. In indirect immunoflourescent assay, it was found that all had circulating antibodies that attached to the epithelial basement membrane zone of normal human conjunctiva. The antibody bounded to a 205-kd protein in normal human conjunctival lysates in immunoblot assay.

The dose of IVIG was 2-3 g/kg/cycle (divided over 3 days). The cycle was repeated every two weeks until conjunctival inflammation subsided. Once the improvement was stablised, the interval between cycle was lengthened to three weeks for a minimum of six cycles, then lengthen to five weeks if no deterioration. In three patients, the interval between cycles at time of report was six weeks.

The progress of the disease was halted and resolution of the chronic conjunctivitis occurred in all the patients. Maximum benefit was noted and maintained after a minimum of four cycles of therapy, while three patients required 12 cycles before the disease were controlled. The duration of therapy varied from 16-23 months (mean 19.3 months) with no treatment-induced side effects noted. Extraocular mucosal resolution occurred with exception of one patient.

Kawasaki Disease

Speaker: Dr. A. J. Cant

It appears that toxins (for example, exotoxin produced by staphlococci and streptococci) acts as superantigens leading to massive immune activation and then release of inflammatory mediators causing the clinical picture and organ damages.

Important sequels include development of multi-system vasculitis and coronary artery aneurysms.

Use of high dose IVIG and aspirin lead to rapid subsidence of fever, decrease in inflammatory mediators, decrease of coronary artery aneurysm formation (confirmed by double blind controlled trials) with a decline of mortality from myocardial infarction from 2% to 0.1%. Previously there was a belief that the therapy was only effective if it was given in the first 10 days of the illness; and if given later than that, a paradoxical harmful effect due to hyperviscosity might arise. More recent studies showed that such belief and worry were not supported.

It is still unknown whether one should give subsequent IVIG therapy when the initial infusions are not fully effective, whether concomitant administration of corticosteroid is of benefit, and the role of antibiotic if Group A streptococcal infection is documented.

Chronic Urticaria

Speaker: Prof. M. W. Greaves

Ten patients with marked chronic urticaria having an autoimmune basis were treated with IVIG 0.4 g/kg/day for five days.

Nine patients showed benefit. Three patients remained free from attack for three years, three patients showed remission but relapsed at six, eight and 21 weeks after treatment. One patient only showed transient improvement.

Safety and Tolerability of IVIG

Speaker: Dr. T. D. Martin

Virological safety

IVIG are usually produced from greater than 1000 donors per lot. For safety sake, screening of donors, methods of viral separation and inactivation must be used to decrease chance of viral transmission. For screening, only known viruses may be screened and no single method of viral separation or inactivation is totally effective. Some companies rely almost solely on methods of screening while some manufacturers only used methods for viral log reduction without using more proper methods of destroying potential viruses. Three basic methods of primary inactivation are used. They are solvent detergent, pasteurization and B-propiolactone. None of these three methods are totally effective, as each has its own limitation. Therefore additional secondary steps, including incubation at pH 4, addition of pepsin, etc. for viral inactivation are employed by manufacturer. Some firms also utilize separation methods like nanofiltration. In 1994, the German authorities proposed specific logarithmic reductions with multiple steps of inactivation (PEI 1994). However, many manufacturers found difficulty in achieving the standard. Nevertheless, several companies are now able to meet these stringent requirements.

Some viruses are very difficult to kill or eliminate, for example, parvovirus B-19 and Hepatitis A virus. To ensure neutralization, one must ensure the brand of IVIG supplied has adequate antibody levels against these antigens. The neutralization process must be adequately validated by International standard. At present, the validation of these methods of primary inactivation, secondary inactivation and separation is only partially standardized and the information provided by some manufacturers may be difficult to understand. The physician should ask the drug company for clear data with regard to viral safety and consult virologist for clarification of ambiguous information.

Tolerability

There are many possible side effects. Mild ones include headache and backache etc. Many of these can be alleviated by reducing the infusion speed.

Moderate side effects are headache, rashes, arthritis, serum sickness, phlebitis, infusion site severe irritation/necrosis, and anaphylactoid reaction. For products with pH <5, phlebitis and thrombotic complications have been reported. Patients with impaired physiology or neonates may not be able to buffer the low pH well if large doses are used.

Severe complications (increasing numbers found in cases using bigger doses) include aseptic meningitis, acute renal failure, cerebral infarction, myocardial infarction, hyperviscosity, thrombosis, vasculitis, haemolytic anaemia, disseminated intravascular coagulation (DIC) and anaphylaxis. Acute renal failure is more commonly seen in neurological patients using high doses. Hyperviscosity may be related to osmolality of the products and may lead to thrombogenesis. Cerebral and myocardial infarction had been reported in elderly patients. It is suggested that preparations with an osmolality greater than 350 osmols should be avoided in patients susceptible to complication of hyperviscosity. Cases of serum sickness without joint involvement, but with immune haemolysis presenting as DIC and haemolytic anaemia, had been reported. The physicians should ask for the contents of the isoagglutinins, anti-A, anti-B, anti-D of the preparation used.

Conclusion

Product from different manufacturers utilize different viral inactivation steps and have different pharmacological parameters. Though most products appear equally efficacious, the safety and tolerability vary a lot and can lead to marked morbidity and potential mortality. Therefore the physicians must make careful choices. They should also ask for reports of pharmacovigilance studies from the drug firm.

Learning points:

Most of the side effects of IVIG are mild, but doctors should be alert for the potential complications, in regard to both viral safety and tolerability.