

Proven and unproven indications for intravenous immunoglobulins – the pharmacist as a chain link in decision making

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Despite progress in molecular engineering and monoclonal antibody production, human donor plasma components will remain life savers and quality of life improvers for years to come, among them the most widely used being i.v. immunoglobulins (IVIG). Unfolding the package insert of most currently available IVIG preparations in the year 2004, one realizes that in addition to formal, labeled indications, these preparations are at disposal for a number of diseases listed under “possible benefit”. Such wording confers a certain degree of freedom for the physician in prescribing IVIG.

The European and North American Drug Agencies designate proven indications referring to as “labeled”. Strictly spoken, manufacturers are allowed to list labeled indications only if IVIG-efficacy has been demonstrated, i.e. proven, in clinical trials using their own preparations. Such strict and conservative rationale of agencies is prompted by differences in the manufacturing and physico-chemical characteristics of individual manufacturers’ IVIG preparation as well as in the plasma donors population from which the producers isolate IVIG. However, in clinical practice, brands of IVIG are mostly used interchangeably for the same prophylactic and therapeutic objectives and at our hospital we occasionally change from one preparation to the other for the same patient. The side-effect spectrum of IVIG nowadays shifts from brand- to patient-specificity (review in: 1). Patient-specificity (headache, shivering in few patients, but not in others) extends into the elderly, a patient-proportion steadily increasing. Thus decline in renal function and susceptibility to hyperviscosity have proven to be independent factors that account for the elderly’s risk and elderly’s adverse drug reactions, including those to IVIG, tend to be more severe (2). The choice for the right IVIG brand at a given sanitary district, supported by pharmacists, often is a mix of criteria: efficacy, tolerability, extended long term safety that includes lack of infectious disease transmission, price, storage conditions with shelf-live and last but not least ease of preinfusion preparation on the ward. The importance of the solvent/detergent (S/D) treatment of plasma products to achieve lack of infectious agent-transmission including prions has recently been stressed. Several studies that used different strains of transmissible spongiform encephalopathy agents have demonstrated the removal of infectivity by different steps used in the manufacture of IVIG and currently, NaOH and certain enzymes and perhaps S/D might come to inactivate the bovine spongiform encephalopathy agent (3). With viruses, West Nile Virus, coronaviruses and avian influenza virus, to name a few recently discovered ones, it is important to include such treatments as S/D and nanofiltration to not only remove virions of known notoriety but also to remove so far unidentified, over-night appearing ones. The 6 labeled hence proven indications for most preparations are: Idiopathic Thrombocytopenic Purpura (ITP), Primary Immunodeficiency, Secondary Immunodeficiency due to Chronic Lymphatic Leukemia, Pediatric HIV infection, Prevention of Graft-versus-Host Disease in adult Bone Marrow Transplantation, and Kawasaki Disease. To the best of the authors feeling a

preparation efficacious for one of these indications will remain efficacious for the others in most cases. The dosage for these indications and the long-term dependency of a given disease hence the calculated need and approximate amount of IVIG to be held in stock by the pharmacist over the year are quite well established. They span from lower dosages in Primary Immunodeficiency and pediatric HIV (200 mg/kg body weight) to as much as 2 grams/kg in Kawasaki disease – the former with life-long need and the latter hopefully only once or a few times until the disease is cured. In Switzerland, most hospital pharmacies are on one given brand not only because of rebates by the furnisher, but also because of the physicians' ability to accumulate clinical experience with a given preparation.

A certain confusion of ideas exists when using the terms “unproven” and off-label use. At least, the association of the two words “unproven indication” is contradictory, because, should an indication remain unproven, then it is no indication. As yet, an unproven possibility to apply IVIG in a given disease based on experimental evidence, from laboratory-bench, experiment-basis to bedside, might transgress the stage from not yet proven (unproven) to proven. To not remaining stuck in semantics, one ought to clearly state that many of the recently listed off-labeled uses of IVIG are proven indications: Recurrent Spontaneous Abortion, Guillain-Barré Disease and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), Autoimmune Haematologic Coagulation Disorders, Fetal Allo-Immune Thrombocytopenia and Neonatal Hemolytic Disease due to feto-maternal ABO-incompatibility, Myasthenia Gravis and Posttransfusion Purpura to select the most pertinent from this list with 18 entries by the Harvard Medical School affiliates in Boston, USA (4). In many indications, IVIG transfusion takes the place of a proven adjuvant therapy, as an alternative to therapeutic plasmapheresis, rarely as the one-and-only treatment option, like in the labeled indications. Let us put this message in other words: If IVIG become withheld, as an example, from a neonatal icterus baby suffering from feto-maternal ABO incompatibility, the evidence-based pressure to administer IVG does not come from statistical power, but from expert panels which formally approve such indication as proven on the basis of relatively few cases in which the treatment was efficient.

Of the possible indications for IVIG some have made it from the unproven to the proven status using the required criterions of sufficient statistical power in clinical phase II or even phase III studies. Unlike with synthetic drugs at barely limited disposal for clinical studies, the donor-plasma product IVIG remains an expensive and limited source hence placebo-control and randomization are often difficult requirements to fulfill by the study coordinators, but most ethical committees are aware of this. Such studies must be evaluated for potential bias since they implement eligibility screening that excludes patients at high risk of morbidity and mortality. In these trials, disease rates and death rates for the study population can rise rapidly during follow-up as the effect of screening wanes and during the open-labeled follow-up, a preponderance of patients may switch to the new therapy. (5). The Cochrane data base system has recently proven extremely valuable since it works with meta-analyses that encompass studies performed not only in the developed world, but also studies performed in less-rich countries where IVIG are important in preventing outbreaks of such diseases as avian flue or corona virus of SARS with consequent risk for global spread. The Cochrane system thus serves the treating physician a valuable tool to decide on using IVIG in such rare but important questions as preventing infection in low birth-weight premature infants. We should also take notice that most of the now proven, off-labeled indications have been discovered during the last two decades suggesting that more are to come. With improvement of understanding the different immunopathological processes that

trigger many autoimmune-/inflammatory diseases (www.immune-complex.ch), some researchers look out for more specific treatments than the polyclonal polyspecific IVIG can provide, e.g. monoclonal antibodies. Such an approach is promising in treating transplant rejection or preventing infectious disease with IVIG remaining important adjuvants.

In this authors environment, the pharmacist plays an important role in choice of the appropriate IVIG preparation and in its safety recording. This role forms part of a sequence of health professionals (Figure 1), the pharmacists part not being the weakest chain link on the stage of selection and adverse experience report. A recent study concerned about quality of drug experience report by pharmacists (6) maintains the prime importance of the pharmacy in this field. Track-keeping of the IVIG lot numbers administered by the pharmacist's client may form part of a computerized database that allows to span infused IVIG preparation lots from the patient back to the plasma donor such as now implemented for labile, cellular blood products.

Legend to the figure

The safety concern for stable plasma products spans from donor selection to postmarketing surveillande/hemovigilance and involves different health professionals

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