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Research Paper

The off-label use of human immunoglobulins in Stiff-Man Syndrome

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ABSTRACT
Aim
Stiff man syndrome is a rare neurological disease characterized by fluctuating stiffness of the chest and limbs, painful muscle spasms, phobia of carrying out actions, tendency to flinch abnormally and ankylosing deformities, such as fixed lumbar posture in hyper-lordosis. Prevalence is estimated at 1 / 1,000,000.
Subject and Methods
The use of intravenous human globulin in the Stiff man syndrome is configured as an off-label prescription of the drug. In this study we investigated patient with Stiff man syndrome treated with IVIG in hospital setting.
Results
In our hospital only one female patient with Stiff man syndromewas treated with IVIG. She immediately showed an improvement in symptoms. Overall, the patient was given 5 courses of treatment during the study period. After each treatment, the patient experienced an improvement in hypertonicity and gait. The amount of costs incurred is equal to € 14291.20 / year.
Conclusion
The hospital pharmacist's role is fundamental both in the preliminary and management activities, in particular into support technical commission. Off-label use in rare life-threatening diseases is configured as a right to health and in the specific case as a right to life and therefore any cost incurred by the National Health System should never be considered excessive.

Keyword
Stiff man syndrome
Compassionate use
Rare neurological disease
Intravenous immunoglobulin (IVIG)

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I. BACKGROUND

Stiff man syndrome (SMS) is a rare neurological disease characterized by fluctuating stiffness of the chest and limbs, painful muscle spasms, phobia of carrying out actions, tendency to flinch abnormally and ankylosing deformities, such as fixed lumbar posture in hyperlordosis(Rakocevic et al. 2019). Described for the first time in 1956 by Moersh and Woltman(Bertorini2011; Lee et al. 2019; Dalakas 2009; McKeon et al. 2012; Khasani et al. 2004), it can manifest itself as a paraneoplastic or idiopathic syndrome (Alexopoulos and Dalakas. 2010). Even today, the cause remains unknown, but an autoimmune pathogenesis is suspected (Dalakas2001).

Prevalence is estimated at 1 / 1,000,000. About 2/3 of the patients are female. Onset occurs around age 45 and symptoms develop over months or years. Progressive muscle stiffness immobilizes the chest and hips, the gait becomes stiff and awkward. The concomitant spontaneous or reflex-induced painful muscle spasms can cause disastrous falls. The fear of crossing open spaces (pseudo-agoraphobia) causes sudden stops in gait, sudden spasms and falls. More recent literature data show that 65% of patients with SNS are unable to carry out their usual daily activities correctly, as a consequence of muscle stiffness, movement insecurity, muscle spasms, etc (Dalakas2001).

There are no focal neurological signs. Clinical variants of the syndrome include stiff limb syndrome (SLS), in which symptoms affect only one limb, and progressive encephalomyelitis with stiffness and myoclonia (PERM), in which stiffness and myoclonic spasms are associated with signs focal neurological. Many patients with SMS, SLS or PERM have comorbidities such as insulin-dependent diabetes mellitus (30%), autoimmune thyroiditis (10%), atrophic gastritis associated with pernicious anaemia (5%); some patients also have breast, lung or colon cancer.

The presence of antibodies against glutamic acid decarboxylase (GADas) in just under 70% of cases suggests an autoimmune pathogenesis. GADas disrupt the synthesis of an inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), which consequently attenuates the inhibition of spinal motor neurons. Diagnosis is essentially based on clinical observation and is confirmed by the detection of GADas in serum and by characteristic electromyographic abnormalities (Alexopoulos and Dalakas 2009; Chang et al. 2013). The potential pathogenicity of anti-GAD antibodies (anti-GAD Ab) remains but still remains uncertain (Rakocevic et al. 2019). Clinically anti-GAD Ab is associated with SMS, type 1 diabetes mellitus and other autoimmune diseases (Lee et al. 2019).

Spinal cord tomography is useful for ruling out other mechanical causes, such as herniated disc or spinal cord cyst.

Differential diagnosis is the atypical expression of a spinal cord disease (e.g. multiple sclerosis, cancer), axial dystonia, neuromyotonia, acquired hyperekplexia ('startle' disease) and movement disorders of psychogenic origin (see these terms). Benzodiazepine and blacofen are usually used for symptomatic treatment.

Immunomodulation therapies (corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis) have been proposed with variable results. In most SMS and SLS patients, treatment helps control symptoms. PERM is more difficult to control and does not have a good prognosis.

Scientific evidences demonstrate benefits of Ig in terms of reduction of stiffness, ability to walk, reduction of GAD levels and improvement of quality of life.

Due to their properties, they are used as replacement therapy, immunomodulatory or anti-inflammatory agents [13]. IVIG, as biological therapeutic agents, have been prescribed for over two decades to treat a variety of neuromuscular conditions (Chang et al. 2019; Rakocevic eta l. 2019).

Given the rarity of scientific evidence, a commission of the American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) has drawn up a consensus document on the rational use of IVIG in neuromuscular diseases. The recommendations, based on the strength of the scientific evidence, categorize neurological diseases that are treated with IVIG into 4 Classes (I-IV). Class-I evidence supports the prescription of IVIG in SMS. The current Ig indications are reserved for patients with a poor response to treatment with diazepam and / or baclofen and significant disability (Grade A recommendation; Evidence level Ib) (Zago et al. 2011). Since 1990, the use of Ig has undergone significant changes, mostly an "off-label" use. These indications represent, to date, between 20 and 60% of the use of IVIG.

SMS remains a rare clinically mysterious disease (Alexopoulos et al. 2010), with patients responding to immunomodulatory therapy. A controlled clinical study with intravenously administered Ig demonstrated superiority in terms of efficacy versus placebo in significantly reducing symptoms (Bertorini 2011). The rationale for the use of IVIg is based on the fact that many neurological and neuromuscular pathologies recognize an established or hypothetical autoimmune basis. However, the clinical results obtained are not constant and probably this variability is an expression of the diversity in the pathogenesis of which autoimmunity can be an important causal moment or mere accompanying phenomenon without clinical significance.

II. SUBJECT AND METHODS

The study was carried out from 1 January 2016 to 31 December 2020 in Mater Domini University Hospital in Catanzaro city, Calabria Region, Italy. The requests for nominative prescription (RPN) relating to neurological therapies with IVIG, dispensed in period of study, were extrapolated from the IT management system in use.

Patients were included in the study who:

- Have a diagnosis of Stiff man syndrome;
- Age over 18 at the time of diagnosis;
- Have received more than one treatment with IVIG.

The date of the first prescription of the IVIG was considered as the index date.

Demographic, clinical, laboratory data are routinely included in the patient's medical record whenever the patient enters the facility to receive treatment. The personal and used data have been anonymised in compliance with current privacy regulations.After inclusion in the study, the demographic characteristics of the patients were analyzed (sex, age, diagnosis, pathology, duration, previous and concurrent treatments).

The expense incurred was calculated considering the ex-factory cost (excluding VAT), net of the temporary reductions required by law.

III. RESULTS

Only one patient with neurological rare disease was treated. The patient was female. The diagnosis of SMS was made in the year 2016. At diagnosis time she was 36 years old. She was treated with IVIg, 35g/day for 4 days every 4 months. She immediately showed an improvement in symptoms. Overall, the patient was given 5 courses of treatment during the study period. After each treatment, the patient experienced an improvement in hypertonicity and gait. After 4 treatment cycles there is an improvement in both fatigue and stiffness.

Considering the ex-factory cost net of discounts applied to public structures of the national health system, the daily economic impact of the therapy is equal to € 1786.40 / day. The patient's treatment cycle includes 4 consecutive days of therapy, with a total cost of € 7145.60 / cycle. Overall, over a three-year period, the patient underwent 6 courses of treatment. The amount of costs incurred is equal to € 14291.20 / year. Total value is equal to € 57164.80, for four years of treatment.

IV. DISCUSSION AND CONCLUSION

In our case, IVIg therapy proved to be safe and effective for the patient with SMS. No adverse event related to IVIg administration was found. According to the data reported in the study by Dalakas et al (2001), the administration of IVIg resulted in an improvement in muscle function and a reduction in rigidity.

The use of IVIg in the SMS is configured as an off-label prescription of the drug, supported by valid scientific evidence in the literature. Only one study attempted IVIg treatment in 16 patients. improved stiffness in 11 patients. The effectiveness, however, was lost in 6-12 months. It is concluded that IVIg have a second-line indication when traditional therapy with valproate, diazepam and baclofen does not obtain satisfactory results (Dalakas et al. 2001; Duse et al. 2009).

Pharmacological prescribing is currently the subject of great interest in the field of professional liability, especially when considered off-label. Off-label use concerns the use of the drug according to different therapeutic indication, dosage, administration, group of patients, compared to those for which it has obtained marketing authorization (AIC) by regulatory bodies (Dooms et al. 2016).

The off-label prescription is regulated in Italy by Law 648/1996 (Minghettiet al. 2017). is complex both for the need to fulfil the obligations imposed by regulatory bodies and for the acquisition of consent from the family. the latter represents a significant moment that is not always easy in very fragile therapeutic relationships (Davies et al. 2017).

An opportunity for discussion on the subject between clinicians, pharmacists and health managers, involved with different roles and skills in off-label prescribing. Reflections and proposals emerge: the usefulness and applicability of the protocols, the feasibility of multicentre studies, the search for a dialogue between doctor and pharmacist that translates the formal act of the off-label prescription request into the sharing of appropriate treatment paths, effective and safe.

It is important to verify the correct use of off-label drugs in complex pathologies, such as neurological ones, by evaluating the scientific evidence to avoid treating patients by wasting resources, but above all by avoiding ethical and safety problems (Mallarini2011). There are, however, also risks associated with off-label use of the drug. Clinical evidence is often lacking to demonstrate its quality, safety and efficacy and, above all, risk analyses conducted by regulatory agencies (Gupta and Nayak 2014; Weynantset al. 2010). Studies published in the literature tend to publish more positive experiences related to off-label use and fewer negative data recorded (Egualeet al. 2016; Saived et al. 2015).

For the purposes of the regular delivery and provision of approved therapies, the role of the hospital pharmacist in the preliminary and management activities (De Fina et al. 2020) as well as support to the technical commission is fundamental:

- assessment of the prescriptive adequacy,
- delivery and monitoring of therapies,
- elaboration of evaluation forms,
- pharmacoeconomic analysis,
- activation of the procedures necessary for procurement,
- examination of follow-up data and their archiving,
- traceability of expenses (Serio et al. 2014).

The off-label use of IVIg in neuromuscular diseases has radically changed the prognosis of patients with degenerative and rare neuromuscular diseases. It can be said that today all autoimmune and neuromuscular diseases, due to their disabling and evolutionary characteristics, are the object of therapeutic attempts with IVIg.

The off-label use of medicines can often be a valid therapeutic option in the control / reduction of symptoms in complex patients. It represents a precious opportunity to significantly improve the knowledge and

therapy of some pathologies. The off-label use of the drug, on the other hand, must be supported and justified by valid scientific evidence from accredited national and international literature (Minghettiet al. 2017). In rare and orphan diseases, for which there are major difficulties in the clinical development and registration process of new drugs, in particular in the organization of pivotal studies with adequate sample sizes, off-label use represents an opportunity for patients (Dooms et al. 2016).

Off-label use in rare life-threatening diseases is configured as a right to health and in the specific case as a right to life (Davies et al. 2017) and therefore any cost incurred by the NHS should never be considered excessive. In Italy, the Government Body (AIFA) approved the off-label use of therapy in the SNS and the total cost of the treatment was fully reimbursed by the NHS. In consideration of the value of life, the quality of life and the high cost of preparations, there is a need to bring order and review the scientific evidence in this regard (Rodriguez-Monguioet al. 2017).

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