Intravenous immunoglobulin and Sjögren Syndrome

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Abstract

Sjögren Syndrome (SS) is an auto-immune disorder with a high incidence and prevalence, variable clinical manifestations and well-defined diagnostic criteria. Increasing attention has been devoted to areas like its pathological mechanisms and the search for new therapeutic strategies. Intravenous immunoglobulin (IVIg) is indicated for many disorders, and investigation on its mechanisms of action has yielded some preliminary findings, especially on its effects on the immune activity. The spectrum for its therapeutic use, although very controversial, has been increasing, mainly in situations involving auto-immune processes. There are a few written cases on the use of IVIg in the SS's treatment, especially when neurological manifestations occur. In this paper we review the interest of using IVIg in SS, and analyze the published case reports of its use. We find that IVIg seems an important therapeutic option for many cases of SS. Accumulating data suggests a rational for its use as second line option in cases of extraglandular manifestations resistant to conventional treatment.

Key words: Sjögren Syndrome, Intravenous Immunoglobulin, neuropathy.

Introduction

Sjögren's syndrome (SS) is an auto-immune chronic disease featured by an exocrine glands dysfunction, associated to xerostomia and xerophthalmia. Often, it is followed by extraglandular systemic manifestations. It can occur in isolation (primary SS) or associated to other auto-immune diseases (secondary SS).[1,2] Physiopathological mechanisms are yet to be clarified being a constant study target, enabling to understand new therapeutic options.[3] One of these is intravenous immunoglobulin (IVIg) having, to date, just a few reports of its use in clinical cases. In 2007, Thanou-Stavrak A and James J., in a review over the treatment of primary SS, refer its use in some clinical manifestations.[3] The costs associated to this therapeutic option are still very high,[4] what makes pertinent a criterious appreciation of its indications, in a context of eventual uncertainty relating with the reachable results.

This paper aims, therefore, to review the role of the IVIg as a therapeutic instrument in SS. Case reports published to date and literature debating the indications for use were assessed. It is still aimed, to get to know the mechanism of action, which starts to be more extensively studied, the recommended posology and the safety profile.

Sjögren's Syndrome

SS is more common among women.[1,2] Primary SS has two incidence peaks: from 20 to 30 years of age and in the sixth decade of life.[5] Primary SS incidence in the general population varies from 1:100 to 1:1000 and its prevalence is estimated from 0.1 to 0.6%.[3] Secondary SS is present in 30% of patients with auto-immune diseases.[2]

SS pathophysiology mechanisms are far from being clarified. It is thought they have multifactorial origin, having environmental factors modulating genetically predisposed individuals. SS is characterized by a lymphocytary infiltration of the exocrine glands and a generalized B lymphocytes hypereactivity.[1,2] An explanatory model suggests that an initial factor (for instances, a viral infection) may cause a cellular death and SS-A protein expression in the surface of gland cells, due to apoptotic cell RNA interaction. Cytokines would be produced and there would be a migration of lymphocytes and dendritic cells to the glandular tissue, producing antiprotein SS-A antibodies. Immunocomplex formed by the link to ribonucleoproteins would be linked to dendritic cells Fc receptors. The

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perpetuation of the local inflammatory process would conditioned the destruction of the glandular tissue, committing the secretion. Genetically predisposed individuals seem to be those with HLA-DR3.[5]

SS shows itself in a pleomorphic fashion with a usually slow progression. If, on one hand, it can only exist limited auto-immuno exocrinopathy, being more common the manifestations of xerophthalmia e xerostomia, on the other hand it can emerge a serious systemic disease with multiorganic manifestations.[6] Systemic vasculitis is considered the main cause of death in patients with primary SS, through the involvement of the Central Nervous System (CNS) or leading to gastrointestinal perfuration.[6] Among the diverse clinic manifestations it is to be highlighted the neurologic and hematologic. When the CNS is reached, neurologic and/or psychiatric conditions can arise. It is thought that such involvement may be related with a lesion by direct immunologic mechanisms, vasculitis procedures[7] or both. The involvement of the peripheral nervous system (PNS) occurs in about a quarter of patients, being showing mostly as a peripheral sensorial neuropathy. More rarely, autonomous nervous system changes can occur (ANS).[7,8]

Hematology complications occurring frequently include: cytopenia, hemolysis, medullary changes and lymphoproliferation. Changes with the increase on the erytrocytary sedimentation rate or hypergammaglobulinemia have been associated to SS[6,9]. The more common lymphoproliferative process is a Cell B non-Hodgkin lymphoma, with incidence of 1-10%[6], locating itself, in most cases, in the salivary glands and in other mucosa associated lymphoid tissues (MALT).[10]

Apart of those referred, there is a set of other extraglandular manifestations.[8] These can be divided in peri-epithelial and extra-epithelial. Patients with mainly peri-epithelial lesions, as interstitial nephritis, hepatic or pulmonary disease, have generally a less serious progression. The extraepithelial involvement, as in the case of glomerulonephritis, polyneuropathy, purpura and vasculites, together with the lymphoma is associated with a worst prognosis.[6]

Diagnosing the Sjögren's Syndrome

The classification criteria were developed and validated, from 1989 and 1996, by the American-European Consensus Group on Classification Criteria for SS, and widely accepted (*Table I*).[11] Due to its high sensitivity and specificity it is used as diagnosis criteria, both from Primary SS as Secondary SS. Primary SS occurs in patients without a potentially associated disease and can be defined in two ways: by the presence of any 4 out of the 6 items mentioned in the *Table I,* as far as item IV or VI are positive, or by the presence of any 3 of the 4 items of objective criteria (III, IV, V, VI). Secondary SS occurs in patients with a potentially associated disease (for instance, another connective tissue disease), being diagnosed by the presence of the item I or II in addition to any 2 among items III, IV and V.

For the SS diagnosis there is yet to be excluded the following conditions: radiotherapy history in the head and neck, C hepatitis, acquired human immunodeficiency syndrome (AIDS), pre-existing lymphoma, sarcoidosis, graft versus host disease and the use of anticholinergic drugs (during at least four times the drug half-life).[11]

Sjögren's Syndrome Treatment

Primary SS treatment varies from local measurements (for instances: humid environment, artificial tear drop) for exocrine deficiencies, immunomodulator drugs in a serious disease with a multiorganic involvement up to the oncologic therapy directed to lymphoma[6]. Secondary SS treatment includes, besides these ones, the necessary measurements to the primary control pathology.[12]

Conventional treatment of systemic manifestations

Corticosteroids are the first choice for the treatment of most systemic manifestations. They are used, for instances in arthritis and serious cutaneous and constitutional manifestations, as well as cytopenias, in isolation or in association to other immunosuppressors. Apart of its most common secondary effects, it leads additionally to quicker evolution of the periodontal disease and oral candidiasis[6]. Corticosteroids are the first line therapy in neurologic manifestations. In a second line there is the option of non-steroidal immunosuppressives and there are still additional therapy options, as cyclophosphamide, azatioprine, hydroxychloroquine or methotrexate.[5,6]

Hydroxychloroquine has been used with success on the treatment of constitutional and musculoskeletal symptoms, as well as non-vasculitis cutaneous lesions.[2,5]

TABLE I

Classification Criteria (American-European Consensus Group [11])

I. Eye symptoms: ≥ 1 of the following:
1. Daily eye dryness troublesome and persistent >3 months.
2. Recurring sensation of sand or burning in the eyes.
3. Tear drop replacement >3 times/day.

II. Oral symptoms: ≥ 1 of the following:
1. Daily feeling of dry mouth >3 months.
2. Salivary glands tumefaction (recurrent or persistent) in adult age.
3. Frequent ingestion of fluids to help swallowing dry foods

III. Eye signs: positive result ≥ 2 following tests:
1. Schirmer Test I, performed with anesthesia (≤ 5mm in 5 minutes)
2. Score with Bengal Rose Test or Score with another eye colorant (≥ 4 according to van Bijsterveld's score)

IV. Histopathology: focal lymphocytic syaloadenitis in the smaller salivary glands (obtained from the mucosa with normal appearance), evaluated by an experienced histopathologist, with a focal score ≥ 1, defined as a lymphocytic focal number (adjacent to mucosa acines of normal appearance and having more than 50 lymphocytes) per 4mm2 of glandular tissue.

V. Salivary glands involvement: objective evidence of its defined involvement by a positive outcome in ≥ 1 of the following diagnosis tests:
1. Non-stimulated total salivary flow (≤ 1.5ml in 15 minutes)
2. Parotid syalography showing diffuse sialectasie, without evidence of obstructing the main ducts
3. Salivary scintigraphy showing a delayed caption, reduced concentration and/or delayed excretion.

VI. Antibodies: presence in the serum of antibodies against RO antigens (SS-A) and/or antigen La (SS-B).

Methotrexate is also used in cases of polyarthritis.[2,6]

Cyclophosphamide is a therapy option that can be useful in glomerulonefritis[6].

Regarding SS systemic manifestations, there is not yet a consensus about the ideal moment to start therapy. According to Soliotis et al, among the cases with neurologic manifestation, those who presented a stable condition, self-limited, do not need any intervention, opposite to cases of progressive disease or with activity signs, where aggressive treatment should be started.[7]

SS non-conventional therapy

There is a growing interest in new therapeutic agents, and these may be of known use, as plasmapheresis, with a less known use, as rituximab, α interferon and IVIg, or is in a study stage, as for instance, leflunomide now in a Stage 2 study.[12,13]

Plasmapheresis is one of the used options when there is a worsening of the neurologic symptoms or when these do not respond to conventional therapy getting an earlier effect, before the beginning of the immunosuppressor effect.[6] It is referred the plasmapheresis in the treatment of complicated SS by hyperviscosity syndrome, hemolytic anemia, thrombotic thrombocytopenic purpura and glomerulonephritis occurring in pregnancy.[6]

Rituximab has been used in non-Hodgkin lymphoma cases associated to the SS, getting a lymphoma remission or stabilization and a SS signs and symptoms improvement. It can be used in monotherapy or combined with chemotherapy.[6,14]

Intramuscular α interferon has demonstrated also a benefit in cases of sensoriomotor and ataxic sensorial neuropathy. It also has an effect on the exocrine insufficiency symptoms, antibodies titles and salivary glands histology.[15,16,17]

IVIg has emerged as a promising therapeutic option, and it seems important to review on this subject.

IVIg

IVIg is a blood product made up by IgG immunoglobulins, having been used for the first time in autoimmune diseases, in the treatment of children with idiopathic thrombocytopenic purpura, in 1981[18].

At present, is an immunomodulator used in several immunologic and inflammatory diseases[19,20]. As it demands sophisticated techniques to get it, its use has been limited by its expensive cost.

Action mechanism

IVIg action mechanisms are not yet well known. It seems there are at present 5 hypothetical action mechanisms. One of them consists in the interaction with the Fc receptor and the subsequent inhibition of the macrophagic phagocytosis.[21] Other action mechanism would be the auto-antibodies metabolism. A high antibody quantity administered would stimulate the host complement system, leading to an increased removal of the former.[22]

The IVIg can also regulate the immune response, reacting with membrane receptors in cells T, B and monocytes.[23]

Lastly, at the CNS level, it is thought that IVIg can also have an anti-inflammatory action reducing the capacity of T cells activated to capture microglia, reducing the levels of tumoral-α and interleukin-10 necrosis factor.[24] At the ANS level, in individuals with auto-immune diseases, IVIg has neutralized the M3 muscarinic anti-receptor activity *in vivo* having increased the vesical and intestinal symptoms.[25]

Nimmerjahn F and Ravetch JV have demonstrated that IVIg anti-inflammatory activity can be due to an IgG minority glucose form, what would explain the need for IVIg high doses. According to this second hypothesis, a recombining IVIg totally composed of IgG hypersyalated would be a potent anti-inflammatory agent for auto-immune diseases.[26]

Posology

Regardless of the SS manifestations type and the dose of 2g/Kg body weight given in five consecutive days (400 mg per day) is the most consensual. Therapy can be kept through the repetition of this cycle at 3-4 weeks intervals, for three to six months.[19]

Safety

Most adverse effects are light and transitory. Include on frequency order, headache, fever, chills, fatigue, nausea, diarrhea, changes on the blood pressure, tachycardia, anaphylactic and allergic reactions. Serious adverse effect include acute kidney failure, thromboembolism and myocardial acute enfarction.[27,28] Katz U et al describe the risk factors to the occurrence of such effects and explain the best way of treating them. Risk factors for the development of acute kidney failure are a pré-existing kidney disease, scarce hydration, age over 65 years old, diabetes mellitus, hypertension, hyperviscosity and a simultaneous treatment with other nephrotoxic drugs. Thromboembolic events have as main risk factors atherosclerosis, advanced age, previous thromboembolism, immobilization, diabetes mellitus, hypertension, dyslipidemia, or administration of an IVIg high dose to a rate of rapid infusion. The same authors, to verify the frequency of adverse effects, have studied a sample of 56 patients treated with IVIg due to different auto-immune conditions, being that 36% had adverse effects.[27]

To minimize the risk of adverse effects must be a careful selection of patients, avoiding administering IVIg to those with a risk multiple factor, and IVIg must be slowly administered (400mg/Kg/day, in less than eight hours, for five days). The pre-treatment with analgesics, non-steroidal anti-inflammatory, anti-histaminic or intravenous corticosteroids may be beneficial.[27]

More rare adverse effects include aseptic meningitis, neutropenia, auto-immune hemolytic anemia, cutaneous reactions (dermatitis with skin scaling in the palm of hands and feet) and, very rarely, arthritis and pseudo-hyponatremia.[27]

Use of IVIg in SS

Some SS manifestations have been approached resorting to IVIg. A literature review was made, in reference search engines, with the expressions: SS, pathophysiology, clinical manifestations, treatment, intravenous immunoglobulin, indications, action mechanism and neuropathy, following the main articles found. We had access to 12 articles describing a total of 17 cases of using IVIg in the SS treatment. It is about patients with SS diagnosed or probably, 14 of them with peripheral neuropathy,[29-37] one with non-erosive arthritis,[38] one with hematologic changes[39] and another with non-erosive arthritis and hematologic changes.[9] In cases with peripheral neuropathy this was sensorial or mainly sensorial, being that in 9 (out of 14) showed a serious sensorial ataxia with gait involvement.[30-34] Three out of the 14 cases of neuropathy have demonstrated also dysautonomia.[29,35,36]

In the *Table II* it is shown a list of reviewed clinical cases. There are an equal number of men and women. The average age in such cases was of 58 years of age,

TABLE II

Clinical cases

Reference	Case	Gender/Age (years)	Extraglandular manifestations
29	1	M/67	CKF; peripheral sensorial neuropathy, dysautonomia.
30	2-6	F/61 F/71 F/57 F/45 F/70	Chronic severe sensorial ataxia with a minimum muscle weakness.
31	7	F/35	Severe sensorial ataxia with a minimum muscle weakness.
32	8-9	F/62 M/69	Sensorial-motor polyneuropathy with marked ataxia.
33	10	F/66	Polyneuropathy essentially sensorial, distal and chronic.
34	11	M/41	Polyneuropathy essentially sensorial, distal and chronic.
35	12	M/37	Dysautonomia.
36	13	F/70	Peripheral polyneuropathy with proprioceptive ataxia, dysautonomy, epilepsy.
37	14	M/81	Sensorial ataxia
38	15	M/39	Non-erosive arthritis (wrists, metacarpophalanges, proximal interphalangic, knees and elbows).
39	16	M/56	Anemia and thrombocytopenia due to myelofibrosis.
9	17	F/63	Neutropenia; hemolytic anemia; thrombocytopenia; non-erosive polyarthritis

F: female gender; M: male gender; CKF: chronic kidney failure.

with a minimum of 35 and a maximum of 81 years old. Apart of the glandular manifestations common to all, Table II shows extraglandular manifestations. In a search made at the Índex das Revistas Médicas Portuguesas [Portuguese Medical Magazine Table of Contents] it was not found any case described of using IVIg in SS.

Therapy scheme

The conventional treatment in 17 cases *(Table III)* was very heterogenous, as 4 patients were not under conventional treatment,[30,32,37] to different corticotherapy schemes, whether isolated (3 cases)[29,30] or in combination with other and diverse options (4 cases)[34,35,36,39]. In most cases, IVIg was administered in 400 mg/kg/day cycles for five consecutive days.[29-32,35,36,37] In the 17th case, it was given a dose of 0.5g/day, also in five consecutive days.[9] Patients in cases 10th and 15th were given higher doses (30 to 34 g/day, in five consecutive days cycles).[33,38]

Clinical progression

In order to make easier the understanding of IVIg treatment effects, we can classify the same in good response with a quick effect (up to two weeks) and/or delayed (for, at least, six months), in intermediate response (when there was a favorable response, without being seen the previous conditions) and in the absence of response *(Table IV)*. Out of the 17 cases, there was a good response in 15, highlighting quick and long lasting responses. In the cases with a record of the effect onset, cases 10th and 14th had the quickest response (in two days).[33,37] In those where it is mentioned the effect duration, case 7th had the longest clinical improvement (for five years).[31]

It was reported only one case with a side effect (case 6), in which neutropenia occurred.[30] Case 13th[36] was not successful, perhaps because it is a much more complex condition, with many diverse manifestations. IVIg had a better effect when used in monotherapy, while the results when used con-

TABLE III

Treatment

Case	Conventional treatment (CT)			IV Ig			
	Therapy	Dose	Duration	Dose	Duration	Overlapping with CT	Time after TC
1	PSL oral	10-20mg/d	NS	0.4g/Kg/d	5 d (3 cycles)	Always	NA
2	PSL	NS	NS	0.4g/Kg/d/5d every 2W	NS	No	NS
3	None	NS	NS	0.4g/Kg/d/5d every 2W	NS	No	NS
4	PP/PSL	NS	NS	0.4g/Kg/d/5d every 2W	NS	No	NS
5	PP/PSL	NS	NS	0.4g/Kg/d/5d every 2W	NS	No	NS
6	PSL	NS	NS	0.4g/Kg/d/5d every 2W	NS	No	NS
7	PSL	60mg/d	5 M	2g/Kg followed by 1mg/Kg/month	12 M	No	NS
8	None	NA	NA	2g/Kg/5d followed by 0.4g/kg every 3 W	NS	No	NA
9	None	NA	NA	2g/Kg/5d followed by 0.4g/kg 1x week	NS	No	NA
10	Pain killers Prednisone	60mg/d	6 M	30g/d 34g/d	5 d 5 d	2 W	NS
11	Corticoids Methotrexate	NS	NS	5 cycles		No	NS
12	Prednisone Hydroxychloroquine Fludrocortisone	0.5mg/Kg/d	2 M	400mg/Kg/d IVIg every 4 W 200 mg/Kg/d every 4 W	5 d (3 M) 5 d (2 M)	No	2 M
13	PSL Azatioprine Methylprednisolone Cyclophosphamide	1 mg/Kg (weaning off up to 10mg/d) 100mg/d 500mg/d 1g/course	18 M 10 M 5 d 2 courses	400 mg/Kg/d	5 d (2 courses)	NS	NA
14	None	NA	NA	400 mg/Kg/d	5 d	No	NA
15	NSAIDs PSL	>30mg/d	NS	30g/d	Days 1-4, 21-24	No	NS
16	EPO Corticoids	NS	NS	2mg/Kg/2days followed by 3 cycles at 3 W intervals	NS	No	1 year
17	Oral corticoid	2mg/kg/d	NS	0.5 g/d	5 d	No	15 d

NA: non applicable; NS: non specified; PSL: prednisolone; PP: plasmapheresis; MCF: metacarpophalangic; IFP: proximal interphalanges; NSAIDs: non-steroidal anti-inflammatory; EPO: erythropoietin

comitantly with other therapy were less satisfactory, namely in case 1 (concomitant administration with prednisone and a second cycle of ineffective IVIg)[29] and in case 13 (concomitant administration with methylprednisolone and cyclophosphamide).[36] In cases where conventional therapy was not used previously

to the IVIg treatment (cases 8, 9 and 14)[32,37] there was a marked clinical improvement, similar to others who received such therapy.

Discussion

In the set of assessed cases, the distribution of the female and male gender did not match the literature referred to the SS.[1,2] The same did not happen with the age distribution, once the average of 17 cases is in line with the SS second incidence peak [6]. Both can be due to the fact of being a convenient non-random sample.

IVIg seems to present good results in SS patients associated to debilitating chronic sensorial polyneuropathy, incapacitating non-erosive arthritis and hematologic anomalies, having been used in high doses. In the few cases higher doses than recommended have been used, it did not seem to exist apparent differences in the clinical condition progression, what leads one to think that higher doses than the recommended/usually used does not seem to bring an additional advantage. The best response to the IVIg treatment in monotherapy and the absence of advantage with the previous use of conventional treatment could lead to think that this could be a first line option. However, to date, there are no indications which enable to predict which patients will respond to conventional treatment. This way, IVIg seems to be a valid therapy option, mainly in cases with refractory extraglandular manifestations to corticotherapy or other conventional therapies. Although it is considered well tolerated, there must also be considered its potential side effects, selecting the patients which might benefit from its use.

TABLE IV

IVIg treatment effects

Case	Effects on the disease (according to the authors)	Comment on the Response *
1	1st cycle: frank improvement (except thermography) 2nd cycle without effect. 3rd cycle: clinical improvement comparable to the 1st.	Good
2	Favorable clinic evolution	Good
3	Favorable clinic evolution	Good
4	Favorable clinic evolution	Good
5	Favorable clinic evolution	Good
6	Subjective improvement of standing up stability, without objective changes, except the gait.	Good
7	Independent deambulation.	Good
8	Unequivocal improvement of the neurologic signs and frank improvement of gait and functional condition.	Good
9	Improvement on the neurologic signs and dryness.	
10	Symptoms disappearing.	Good
11	Improvement on the symptoms and normalization of neurophysiologic studies.	Intermediate
12	1st cycle: increase on orthostatic BP, kept for 3 weeks. Recurring episodes of syncope and orthostatic hypotension after 5 A. 2nd cycle: clinical improvement	Good
13*	Without improvement	Absent
14	Clinical improvement	Good
15	1st cycle: increased improvement on arthritis and glandular symptoms. After 3 months there was a recurrence of moderate arthralgia. On the 6th month there was a severe arthritis. 2ndt cycle: frank improvement of symptoms.	Good
16	Increase on Hb and platelets levels.	Good
17	Increase on neutrophil count.	Good

Hb: hemoglobin; BP: blood pressure; *according to classification presented in text

The good response to the majority of the cases described, with improvement of the quality of life in a short while and for a long time after its use, can justify its use in spite of the high cost. It should be noticed, however, that in a recent review on the IVIg use, it is not mentioned its use in SS patients[19]. However to assess its therapeutic and safety effects, it

emerges the need for controlled prospective studies with good sampling.

Conclusion

SS is a frequent auto-immune pathology, with several manifestations, among which polyneuropathy, extra-glandular manifestations in joints and blood who were treated with endovenous human immunoglobulin with promising results.

There is a need for cohort studies with defined and homogenous criteria for all the patients, in a way to be possible to draw definitive conclusion on whether it is beneficial to use IVIg in SS treatment due to its high cost. The low risk associated is confirmed in literature, and it seems that it is already justified its use as a second line therapy in SS situation with refractory extraglandular manifestations refractory to corticotherapy or other conventional therapies. ■

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