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Review

Real life use of prostacyclin analog (Iloprost), a multicentric survey data from the scleroderma study group Emilia Romagna (Sclero-RER) and review of the literature

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Abstract. *Background and aim*: Iloprost is recommend worldwide for the treatment of RP and the healing of DUs. The aim of this study is to report the regimens of Iloprost administered in different rheumatological centers within the same regional Health System Methods: A questionnaire exploring different items related to the use of Iloprost was developed and reviewed by three expert rheumatologists. The questionnaire was distributed as an online survey to all local SSc referral centers in Emilia-Romagna (Italy). Data are reported as percentage or median with interquartile range (IQR), as appropriate. An updated review of world literature on this topic was also carried out. *Results*: All the invited centers completed the survey. There were both local (8) and university hospitals (4). The majority (58%) had a rheumatologist as head physician. All centers used Iloprost: a single monthly administration was the most common treatment (75%). The cycle lasted 1 [IQR 1-2] days with a 0.5-2.0 ng/Kg/min dose according to the drug tolerance of the patients. There were overall 68 spots (beds, reclining armchair, or simple armchair); 2.0 [1.5-4.0] patients were able to receive Iloprost at the same time. University Hospitals had more physicians at their disposal than local hospitals but less paramedic personnel (respectively: 1.8 vs 1.2 physicians, 1.5 vs 2.1 nurses). *Conclusions*: These observations were in line with the majority of previous studies reporting different regimens, comparing similar (but not identical) dose and schedule administration, however, despite differences being at times substantial, no standard infusion method is yet available. (www.actabiomedica.it)

Key words: scleroderma, digital ulcers, prostanoid, Raynaud phenomenon

Introduction

Systemic Sclerosis (SSc) is a complex autoimmune disease characterized by vascular damage, immune activation and fibrosis of skin and internal organs (1). Raynaud phenomenon (RP) is frequently the first symptom of the disease and growing evidences are supporting the hypothesis that SSc may be a vascular disease, with a pivotal role of endothelial cells (ECs), particularly in the very early phase (2,3). Unknown triggers, such as micro-organisms and environmental toxics, may induced local stimuli to endothelial cells promoting inflammatory response and subsequent vasculopathy and fibrosis. Capillary and small vessels, which are the main regulators of blood flow resistance in the circulation, are most commonly involved in SSc vascular defects. Abnormalities seen in these vessels comprise gaps, vacuolization, and eventual destruction of ECs. Perivascular fibrosis and immune cells infiltration, mainly macrophages and lymphocytes, can be found as well (4). Functional and structural deficit in SSc patients include increased vascular permeability, reduced Nitric Oxide (NO) activity, impaired angiogensis, endothelial to mesenchimal transition and lower VE-cadherin expression (5). Iloprost (IP) is synthetic analog of prostacyclin (prostaglandin I_2 [PGI_2]) and preserve PGI_2 vasodilatory and antiplatelet effects having a better stability, longer half-life (20-30 minutes) and better solubility. Intravenous Iloprost is licensed across Europe for different indications, including RP and the healing of digital ulcers related to SSc, and the European League Against Rheumatism (EULAR) (6) enlisted it as a primary treatment option (grade A recommendation). IP stimulate adenylate cyclase to produce cAMP through the activation of PGI_2 receptors located on smooth muscle cells and ECs. Receptors activation drive to inhibition of smooth muscle constriction and platelet aggregation and promote formation of endothelial adherens junctions and reduced ECs's monolayer permeability. Particularly adherens junctions are responsible for amplifying Nitric Oxide (NO) signaling, inhibit apoptosis and reduced inflammation (5). Even if the importance and the usefulness of IP in scleroderma patients, particularly those with vascular involvement, are universally acknowledged, both therapeutic regimens and indications are extremely variable. In a 2011 review (7) it clearly emerges that IP therapy came inevitably with different therapeutic approach: from drug dosage (ranging from 0.5 to 2 ng/Kg/min), to schedule administration (from one day only to 21 consecutive days) and to interval from one administration to the following (8).

The main aim of this study is reporting how Iloprost is used by different SSc referral centers belonging to the same Health System. Even if the focus is on Iloprost regimens, the investigation includes the assessment of some issues that can influence the drug administration (i.e. personnel, number of spots and how much patients need the treatment). An updated review of the world literature on this topic was also reported.

Patients and methods

This observational cross-sectional study was designed in order to assess the iloprost i.v. regimens that are prevalent in in the real-life practice. It is carried out following the Declaration of Helsinki principles. The local Ethics Committees approval was not necessary as there was no patients' participation.

Survey

Three rheumatologists (DG, AA, FG) expert in RP and DU related to SSc treatment proposed a series of items / questions exploring the iloprost i.v. modality of administration and the healthcare context in which services are provided. Two other rheumatologists (AL, LM) reviewed the questionnaire and prepared an online survey.

Referral centers

All centers with the following inclusion criteria were enrolled: a) belonging to the Emilia-Romagna (Italy) Health System; b) possibility to use iloprost i.v. in outpatient or inpatient clinic; c) at least 5 years in managing RP or vascular complications in SSc; d) more than ten SSc patients followed-up.

For each center, a contact person was selected and asked to fulfill the online survey.

Data collected

The following data were recorded: 1. University/local Hospital, 2. Specialist (rheumatologist vs others), 3. IP use indications (Primary RP, secondary RP, DUs), 4. infusion devices, 5. days of therapy, 6. frequency of administration, 7. IP dosage, 8. therapy spots (calculated as daily available spots), 9. type of spots (chair, reclining chair, bed), 10. dedicated personnel (nurses/doctors), 11. accommodation Y/N (boards and logging), 12. hours of operations, 13. limitation to hypothetical best practice, 14. suggestions for better practice.

Review of the literature

A throughout search in PubMed, Embase, Scopus, Web of Science, Asian Science Citration Index (ASCI), IranMedex, Scientific Information Database (SID), PaKMediNet, IndMed, and Index Medicus for the World Health Organization Eastern Mediterranean Region (IMEMR) regarding SSc patients treated with Iloprost was performed up to June 2022, using the key words scleroderma, systemic sclerosis, iloprost, and prostaglandin.

Analysis

Continuous variables were reported as median value and Inter Quartile Range (IQR); categorical values as percentage.

Results

Survey was fulfilled by 12 sites: 4 University hospital and 8 local hospitals, 7 driven by Rheumatologists and 5 from internal medicine specialists with/without concomitant rheumatologists.

IP is ubiquitously used for SSc-related digital ulcers (SSc-DU) and secondary RP but only a half of sites use it for primary RP. Seventy-five percent of sites (9/12) dispense IP at least once a month, but some other (one each) on weekly basis, every other month or every 7 weeks. Drug administration may last from 2 to 5 consecutive days (median 1, IQR 1-2) with drug dose ranging from 0.5 to 2 ng/Kg/min progressively increased to the maximum tolerated dose and with a minimum regimen variability from site to site. One site only, stratify drug dose on patient body weight: 0.5-1-2 ng/Kg/min respectively for patients under 50, 65 or 75 Kg.

Our regional hospitals may count on overall 68 spots, some available as beds (outpatient or inpatient), some as reclining chair or chair (outpatients only).

University Hospitals count on more physicians than local hospitals but have less paramedic personnel (respectively: 1.8 vs 1.2 physicians, 1.5 vs 2.1 nurses). Our results showed that university Hospitals treat more patients than local hospitals (442 vs 247 per year, or daily 20 vs 19) boasting more daily available spots (29 vs 24) and generally longer hour of operations.

Every site is able to offer meals (except one) and to accommodate from 1 to 12 patients at the same time (median 2.0, IQR 1.5-4.0). Hours of operations generally range from 8 A.M. to 2 P.M. with some centers (6/12) offering an extra time in the afternoon (5 sites every afternoon from Monday to Friday, 1 site on Monday and Thursday only) variable from 1 to 3 hour for the most virtuous site. Every site has facilities for patient with disabilities and can grant wheelchairs locally. Nine sites (85%) administer at the same time calcium channels blockers (eg. Nifedipine), 2 sites (25%) acetylsalicylic acid and one site Low Molecular Weight Eparin.

Available data from the world literature regarding iloprost treatment in SSc patients comprise 27 reports thoroughly summarized in the Table 2 (9-35). We included 7 RCTs (9–15) and 12 open-label uncontrolled trials (16–27), together with retrospective studies (28–35). These studies generally presented small patients' series (from 12 to 131 pts), with the exception of a study reporting the effects of IP in a large series of 346 scleroderma patients (34). The indications to IP treatment were generally Raynaud phenomenon and/or digital ulcers, while the dosage and modalities of drug administration as well as the duration of patient's infusions largely varied among different studies. Following the first description of SSc patients with RP by McHugh et al. in 1988 (13), the majority of the studies focused on the significant amelioration of Raynaud phenomenon and/or digital

ulcers after IP treatment (Table 1). The improvement of Raynaud phenomenon was observed in many studies (10–15,17,19–21,23,28); more recently, two studies also reported the effects of IP treatment in the skin involvement of SSc patients related to an improvement of microvascular functional capacity (27,35). Mazzone et al. similarly demonstrated a reduction of endothelial cells and coagulation cascade activations (36). These cohort studies demonstrated that even if many regimens have been tested, sometimes with substantial differences among them, no data on the superiority of a regimen in terms of efficacy, tolerability or costs for payers were definitely reported.

Conclusions

Robust data promoted the use of IP in SSc patients, particularly those who manifest a prominent vascular involvement (RP, Digital Ulcers, Pulmonary Arterial Hypertension) (8). Thus, more than just one medical society suggest its use in these patients, even with some differences: UK experts suggested the use of IP for SSc patients with refractory vasculopathy while Canadian indicated IP as fourth line treatment (21,37). EULAR guidelines suggest IP use as proved therapeutic strategy for RP (primary and secondary), DUs and Pulmonary Arterial Hypertension (following ESC guidelines) with a grade A strength of recommendation, but IP is considered as a the third line treatment for primary RP (6). Despite this data and recommendations, from the late 80s when first data were published on the use of IP in RP, different regimen where worldwide applied but we are still missing a standardized one based on high quality evidences (13,14,38). In 1994 Wigley et al., published a RCT on the use of oral PA in SSc-related RP and DUs (15). Subsequently, in the next years many other authors published data (RCTs) on the use of IP for the former indications, comparing similar (but not identical) dose and schedule administration. Literature review on this topic is summarize in TABLE 2. In the past forty years so many regimen has been tested and compared but even if differences were sometimes substantial, we are still missing definitive data on the superiority of a regimen in terms of efficacy, tolerability or costs for payers (public or private). Considering that despite different regimen were applied, efficacy has never been questioned, it might be hypothesize that usefulness of IP in RP and scleroderma related vascular complications might be due to IP's pharmacological properties. Mazzone et al., for example, provide evidences that iloprost reduces endothelial cells and coagulation cascade activations. These mechanisms are thought to be responsible for improvement in microvascular functional capacity and for the long-term clinical benefit generally observed (36). Moreover, Giordo et al. provide evidences that sera of iloprost-treated SSc patients failed to increased ROS levels and collagen synthesis, suggesting a potential antioxidant mechanism of this drug (39). More recently Tsou et al demonstrated a pivotal role of IP in reversing vascular dysfunction in SSc. They demonstrated that, besides the well-known anti platelet and vasodilatatory activities, IP promote angiogenesis, reduced monolayer permeability and augment endothelial adherens junctions. Particularly the last activity, increasing adherens junctions, seems to be critical because subsequently promotes amplification of Nitric Oxyde (NO) signaling, inhibited apoptosis and reduced inflammation (5). Based on these recent data seems possible that IP may boast a role as disease modifying drug, but more studies are needed to determine the "better" regimen of administration.

With the "PROSIT", an observational and multicentric study, researchers aimed to investigate the current treatment for SSc vasculopathy with particular interest in IP indications and therapeutic regimens. They concluded that the schedule of IP administration is homogenous among the Scleroderma Units but more studies are needed to discriminate if a given treatment's schedule is superior to alternative regimens (34). For example, in a paper from Milio et al., they compared three different IP regimen (0.5-2 ng/Kg/min once a month vs 20 infusions every 6 months vs 10 days within 2 weeks) and did not find any differences in the outcome measure (total daily duration of attacks express in minute) (19). Schioppo et al. focused attention on evaluating Health-related Quality of Life in SSc patients, treated with two IP different schedules (5 consecutive days every 3 months, or one day monthly) but they did not find any statistically significant difference with respect to quality of

Table 1. Characteristics and behavior of involved Centers administering intravenous prostanoid(s).

	Number of involved Centers: 12	
	N (%)	**Median (IQR)**
Rheumatologist-leaded	12 (100.00)	
University center	2 (16.67)	
Indications		
pRP	6 (50.00)	
sRP	12 (100.00)	
SSc	8 (66.67)	
SSc-DU	12 (100.00)	
Prostanoid chosen		
Iloprost	12 (100.00)	
Alprostadil (off-label)	4 (33.33)	
Location of administration		
DH/DS	10 (83.33)	
Hospital stay	3 (25.00)	
Ambulatory	4 (33.33)	
Home	1 (8.33)	
N° of available accommodations		5.50 (3.50 – 8.00)
Mean of administration		
Infusion pump	11 (91.67)	
Infusion syringe pump	4 (33.33)	
Infonde® pump	4 (33.33)	
Elastomeric pump	1 (8.33)	
Length (day(s)) and frequency (week(s)) of Iloprost cycle(s)		
1 d, every 4w	7 (58.33)	
1d, every 7w	1 (8.33)	
2d, every 4w	1 (8.33)	
3d, every 1w	1 (8.33)	
5d, every 4w	1 (8.33)	
5d, every 8w	1 (8.33)	
Dose of Iloprost		
0,5-2ng/kg/min[1, 2, 3, 4]	12 (100.00)	
Infonde® pump: 1 vial, 25,2mL/24h	1 (8.33)	
Concomitant medication(s)		
CCB	11 (91.67)	
ASA	2 (16.67)	
LMWH	1 (8.33)	

Table 1 (*Continued*)

	Number of involved Centers: 12	
	N (%)	Median (IQR)
Other(s)[5]	3 (25.00)	
Staff		
Physician(s)		1.00 (1.00 – 2.25)
Nurse(s)		1.75 (1.00 – 2.00)
Daily hours of nurse care		7.00 (6.00 – 7.25)
Patient(s) per Center		
Actually treated (total number)		30.00 (20.00 – 50.50)
Daily treated		2.00 (1.00 – 4.00)
Esteemed number of potentially treatable patients		40.00 (20.00 – 50.00)

Data are shown as absolute number (N) and fraction (%) of Centers fulfilling each criterion listed on the left; quantitative variables are expressed as median and interquartile range (IQR) when appropriate. RP: Raynaud phenomenon (p: primary; s: secondary, independently of the underling connective tissue disease); SSc: Systemic Sclerosis; DU: digital ulcer(s); DH/DS: Day Hospital/Day Service; CCB: Calcium-channel blocker; ASA: Acetyl-salicylic acid; LMWH: Low molecular weight heparin. [1]Dose and length (hour(s)) of administration, adjusted according to patient's tolerability; [2]in one case, duration of cycle according to presence/absence of DU; [3]in one case, dose [ng/kg/min] adjusted according to body weight: 0.5 for <50kg, 1 for >50kg and <65kg, 1.5 for >65 and <75kg, 2 for >75kg; [4]in one case, infusion speed reduced if high cardiovascular risk; [5]pentoxifillin and/or aminaphtone.

life (mobility, self-care, usual activities, pain, anxiety/depression, general health status) (26). In another paper, the monthly regimen versus the 5 consecutive days regimen showed different acute effects assessed by means of power doppler ultrasonography and videocapillaroscopy, particularly in those patients treated once monthly. Chronic effect, otherwise, were not detected in either the two subgroup (one monthly infusion vs five consecutive days) (27). The standardization of an IP regimen, based on solid evidences, is for sure an unmet need for rheumatologists and patients.

The aim of our study is to better understand hypothetical hindrances and promote high quality studies to reach this target: a better therapy for patients and a better distribution of resources.

Our survey, for example, revealed that patients potentially to be treated are greatly more than those we are able to treat. Trained personnel are frequently the first limitation (paramedic (6/12 sites) and physicians (3/12) followed by the lack of adequate spots and facilities. Some sites are not even able to offer board and logging and some have limited hours of operations offering continuous infusion only during morning time.

We might assume that intravenous administration has always limited the potential treatment benefit of IP and has somehow limited the development of focused trial to establish the better schedule of administration. It is partially true even if we consider the current indication: every site uses it to promote DU healing, only a half of them prescribe it for primary RP. It is reasonable to hypothesize that even if every site is perfectly aware of the benefits of IP also in the treatment of primary RP, they probably face limitations (spots, personnel…) forcing them to reserve available spots to conditions with worst prognosis (such as secondary RP and/or DU). In this context, the recent appearance of the new portable infusion pump (already used by 4/12 sites) and growing local projects of self-administration at home with the assistance of trained personnel (nurses a couple of time a day), may pave the way to RCTs investigating pros and cons of a continuous infusion regimen vs the others. Home administration may reduce cost items as personnel, board and logging and transportation. In the Covid era, it may also reduce movement, direct personal contact as well as the direct risk of infection which is always valid, regardless Covid-19, even for other infectious diseases which are harmful conditions for immunocompromised individuals.

The present study has for sure its own limits. First, we did not elaborate a pharmacoeconomics analysis. Second, it involved only 12 centers. Anyway they all

Table 2. Iloprost infusion regimens: review of the literature.

Author	Trial design	Infusion Regimen	Regimens comparison outcomes
McHugh N.J. et al 1988 (13)	Double-blind, randomized cross-over trial placebo-controlled, single centre	0.5- 2 ng/kg/min for 6 hours, 3 consecutive days, every 6 week	\
Rademaker M. et al. 1989 (14)	Double-blind, randomized placebo-controlled	0.5 -2 ng/kg/min, for 8 hours 3 consecutive days, followed by 1 day at week 8	\
Torley H.I. et al. 1991 (11)	Double-blind, randomized multicenter	A) Low dose regimen: 0.5 ng/kg/min B) Standard dose regimen: 2 ng/kg/min	Similar reduction of RP severity and duration and ulcer healing. Less adverse events in group A.
Constans T. et al. 1991 (16)	Prospective open label, single centre	0.5-2 ng/kg/min, for 6 hours for 11±7 days	\
Wigley F. et al. 1992 (12)	Double-blind, randomized, placebo-controlled, 2 centres	0.5-2 ng/kg/min, for 6 hours, for 5 days	\
Wigley F. et al. 1994 (15)	Double-blind, randomized, placebo-controlled, multicenter	0.5-2 ng/kg/min, for 6 hours, for 5 days	\
Zachariae H. et al. 1996 (17)	Prospective, open-label, single centre	0.5 - 2 ng/kg/min, for 6 hours 8-13 days	\
Biasi D. et al. 1998 (18)	Prospective, open-label, single centre	0.5-2.0 ng/kg/min, for 6 hours, 5 consecutive days, every 3 months	\
Scorza R. et al. 2001 (10)	Prospective, randomized,controlled, blind observer , single centre	2 ng/kg/min for 8 hours, for 5 days, then 1 day every 6 weeks	\
Milio G. et al. 2006 (19)	Randomized, open-label, single centre	0.5- 2 ng/kg/min for, 6 hours: A) 10 days for 2 consecutive weeks every 3 months B1) 1 day every month B2) 20 days every 6 Months	Total average daily duration RP attacks (min): decreased in all groups ($p<0.01$ between group A and B2 at T6, T12 and T18) Average duration of single attacks RP (min): decreased in all groups ($p<0.05$ between group A and B2 at T12 and T18) Average daily frequency of attacks RP: decreased in all groups ($p<0.05$ between group A and B2 at T6; $p<0.05$ between group A and groups B1 and B2 at T12; $p<0.05$ between group A and B1 at T12; $p<0.01$ between group A and B2 at T18) RCS: decreased in groups A and B1 ($p<0.01$ between group A and B2 at T6, T12 and T18) SF-36: physical aspect, general health, vitality increased in group A > B1 and B2 ($p<0.01$ between group A and B2 at T6, T12 and T18); mental health group A > B ($p<0.05$ between group A and B2 at T6; $p<0.01$ between group A and groups B1 and B2 at T12 and T18)

Table 2 (*Continued*)

Table 2. Iloprost infusion regimens: review of the literature.

Author	Trial design	Infusion Regimen	Regimens comparison outcomes
Balbir- Gurman A. et al. 2007 (20)	Prospective, open-label, single centre	0.5-2ng/kg/min, for 8 hours, for 5 days	\
Kawald A. et al. 2008 (21)	Randomized, open label, single centre	A) 0.5-2 ng/kg/min, for 6 hours B) 0.5 ng/kg/min, for 6 hours, 21 consecutive once or twice a Year	Duration RP/min: significant reduction in both groups ($p \leq 0.001$ in group A and $p \leq 0.0001$ in group B) N RP attacks/week: significant reduction in both groups ($p \leq 0.001$ in group A and $p \leq 0.0031$ in group B) N DU: significant reduction in both groups ($p=0.0005$ in group A and $p \leq 0.001$ in group B) mRSS: significant reduction in both groups ($p<0.003$ at 3 years follow-up)
D'Amelio P. et al 2010 (22)	Prospective, open label, single centre	2 ng/kg/min, for 6 hours, for 5 days, every 28 days	\
Bali G. et al. 2011 (9)	Double-blind, randomized, placebo-controlled, single centre	0.5-2 ng/kg/min for 3 hours, for 5 consecutive days, then once per month	\
Auriemma M. et al. 2013 (23)	Prospective, open-label, single centre	0.5-2 ng/kg/min, for 6 hours, 1-3 days every 30 days, 12-16 weeks of summer therapy suspension	\
Cestelli V. et al. 2016 (24)	Prospective, open-label, multicenter	2 ng/kg/min, 1 day every month	\
Rotondo C. et al 2018 (25)	Prospective, open-label, single centre	0.5-2 ng/kg/min, for 10 h per day, for 3 consecutive days	\
Schioppo T. et al 2018 (27)	Prospective, non-randomized, single centre	A) 0.5-2 ng/kg/min, for 6 hours, every month B) 0.5-2.0 ng/kg/min, for 6 hours, for 5 consecutive days, every 3 months	ILO has acute effect on periungual vascularization at PDUS, especially in group A. No chronic effect at PDUS detectable before the following infusion.
Schioppo T. et al 2019 (26)	Prospective, open-label, single centre	A) 0.5-2 ng/kg/min, for 6 consecutive hours, monthly B) 0.5-2 ng/kg/min, for 6 consecutive hours, for 5 consecutive days C) No Iloprost	No difference in Health related quality of life assessment.

belong to the same regional health system and offer assistance to SSc patients in a pretty unvarying setting. Furthermore, from our data, it is impossible to discriminate whether University Hospital have more potential than local hospitals (except for a slight increase in the number of trained personnel).

The lacking of robust and high quality (e.g. RCTs) data on the best treatment regimen with IP in SSc are probably due to limited resources and to dark sides in the knowledge of IP pharmacology, more than on data and expertise on its efficacy and safety profile. Common efforts are needed to support the use of PA without restrictions and consequently promote high quality studies to evaluate the best indication and the best administration regimen to increase patients' quality of life and better resources distribution.

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Conflict of Interest: Alarico Ariani received honoraria as a speaker and an advisory board member of Amgen, Bristol-Myers Squibb, Boehringer, Bruno farmaceutici, Janssen, Lilly, Novartis, Novo Nordisk, Sanofi and Zentiva. Luca Magnani received honoraria as a speaker from Boehringer Ingelheim. Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: Each author made substantial contributions to the conception and design of the work; L.M., A.A., A.L.M.. and D.G. approved the submitted version (and any substantially modified version that involves the author's contribution to the study).

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