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Propionibacterium Acnes: A Putative Immunemodulating Weapon Against the Coronavirus Impending Epidemy

Palmieri B.[1,2], Vadalà M.[1,2], Bondi M.[3], Cermelli C.[4]
[1]Department of General Surgery and Surgical Specialties, University of Modena and Reggio Emilia Medical School, Surgical Clinic, Modena, Italy;
[2]Second Opinion Medical Network, Modena, Italy
[3]Department of Life Sciences, University of Modena and Reggio Emilia, Italy
[4]Microbiology Department, University of Modena and Reggio Emilia, Italy

Abstract:- The impending coronavirus disease 2019 (Covid-19), and the risk of its worldwide pandemic development requires urgent effective therapeutic procedures, being it orphan of a specific vaccine predictably for the next 24 months or more.

Attempts to treat the infection with some chemotherapies borrowed by other antiviral registered schedules or with other adopted off label drugs are on the way, but our concern is to run against the time adding if possible a further safe, effective sustainable treatment available to the greatest number of people anxiously claiming for prevention or disease control.

We focused on the challenge of an impressive bacterial quick and safe antiviral activity, incidentally observed on advanced metastatic cancer injected on a compassionate spontaneous basis with dead bacteria into the tumor masses (years 1975-79).

The present paper describes the details of our experience namely with *Corynebacterium parvum* which displayed the best effective and safe viral symptoms remission in comparison with BCG and one autochthonous wild strain of *Streptococcus faecium*.

We successfully followed up with this procedure occasionally in the more recent years in some cases voluntarily requiring vaccination after detailed informed consent acceptance, to relieve their aggressive cumbersome viral infections.

The take home message of this report is to take in account not only the excellent new tailored Gene targeting therapies, but, especially in emergency, to do not absolutely forget the old ones!!!

I. INTRODUCTION

The history of *C. parvum* as immunomodulating bacterium is long standing, with a very intensive research publications period between 1960 and 1975 by Halpern, Woodruff et al **[1, 2].** Demonstrated that injections of killed *Corynebacterium parvum* into mice induced a strong and quick stimulation of the reticuloendothelial Network, preventing experimental tumor transplants or inhibiting their growth. Many different *C. parvum* strains have been used along the years in the different laboratories by each research group for immunological studies because of their specific immunomodulatory, antineoplastic, antiviral activity, and the increase of the immunocompetent organs weight; in the experiments of Gil et al **[3]** cr 51 radiolabeled *Propionibacterium* kp45 when intravenously injected was trapped in liver spleen and lungs parenchyma's and cleared out by phagocytosis of the reticuloendothelial cells, thus triggering the immune modulating effect.

This activity is related to the resistance of living or killed bacteria to be phagocytized and digested by the host macrophages, and the peptidoglycans carbohydrates and lipids compositions of the cell wall, make the differences accordingly with the studies of Adlam and Reid, Baum and Breese et al demonstrated after bacteria removal by the reticuloendothelial system, a strong interferon induction and Natural killer cells recruitment; the subcutaneous bacteria administration seems the more effective immunostimulant route while the intravenous and intraperitoneal one can elicit immunosuppressive response **[4-7] .**

As to antiviral activity, Kirchner showed in the normal and immunosuppressed mice protection from herpes virus infection with intravenously injected *C.parvum* **[8-10]**.

Szmigilielski and coworkers with another strain inoculated intraperitoneally strongly reduced from 90% to 30% the mice mortality due to herpes virus encephalitis **[11]**. The same authors showed protection of mice **from varicella and murine hepatitis (due to a coronavirus species) [11].** Kobus and Szimigielski observed an immunopotentiation of some viral vaccines by contemporary subcutaneous injection of *C. parvum*, supporting the hypothesis that this bacterium might be a powerful adjuvant in the vaccines preparation **[11, 12]**. As to the bacteria administration timing respect to the antiviral clinical outcome, in the herpes virus experimental model, protection was achieved when bacterium had been administered 7 days before, but not simultaneously to the viral infections **[10].**

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In the MHV3 experimental model protection was achieved when *C. parvum* was delivered the same day of the viral infection, no matter how many hours if before or after the viral challenge. **Schindler and Budzko** confirmed this administration time schedule in the mice model infected with Jumin virus **[13, 14]**. On the basis of this experimental background we planned to try the *C. parvum* induced aspecific immune stimulation in some severe viral-induced clinical conditions starting from herpes zoster painful and devastating conditions when cycloviran or other effective virus killing therapies were not yet available on the market except the very weak lysozyme remedy and steroids.

For ethical reasons, the very first safety and dose finding investigation was performed of myself, during an herpes simplex lips infection and fever **(Figure n.1)** due to summer sun sudden over- exposure, accordingly with the philosophy of **"the Doctor-Care-Yourself"** Medical Network (see the foot note).

***The Second Opinion Medical Network** is a consultation referral web and Medical Office System recruiting suddenly a wide panel of real-time available specialists, to whom any patient affected by any disease or syndrome and not adequately satisfied by the diagnosis or therapy can apply for an individual clinical audit **[15]**. Due to the doctor-patient communication gap, most of the patients usually wander around the medical websites looking for proper answers to their health problems. However, their search often becomes compulsive and obsessive and often ambiguous and frustrating **[16].** Palmieri et al. [17] describe this borderline or even pathological behaviour as the "*Web Babel Syndrome*" – a psychological imbalance affecting young and elderly patients, especially those with multiple synchronous diseases who receive from their caregivers heterogeneous and misleading informations or advices, including confused, contradictory statements and prescriptions **[18]**. To deal with this problem, the Second Opinion Network aims to be a useful "problem-solving" support revisiting each diagnostic and therapeutic step and properly re-addressing tailored treatments and prognoses, as well as preventing unnecessary investigational procedures and unhelpful and expensive medical and surgical interventions **[19]**.

****The "Doctor-Care-Yourself" Network is intended to** actively monitor the health of hospital doctors, avoiding as much as possible burnout, drug addiction, vices; promote their cognitive optimal integrity, fitness and wellness, multimedia arts performances: stimulate the best empathic doctor –patients relationships, enclose the sick doctors in the same experimental trials as their patients **[20, 21];** promote (last but not least!) preliminary self–made pilot trials individually or in small groups of doctors affected by the same illness (i.e. hypertension, diabetes, morbid obesity, liver steatosis, etc) **[22-24].**

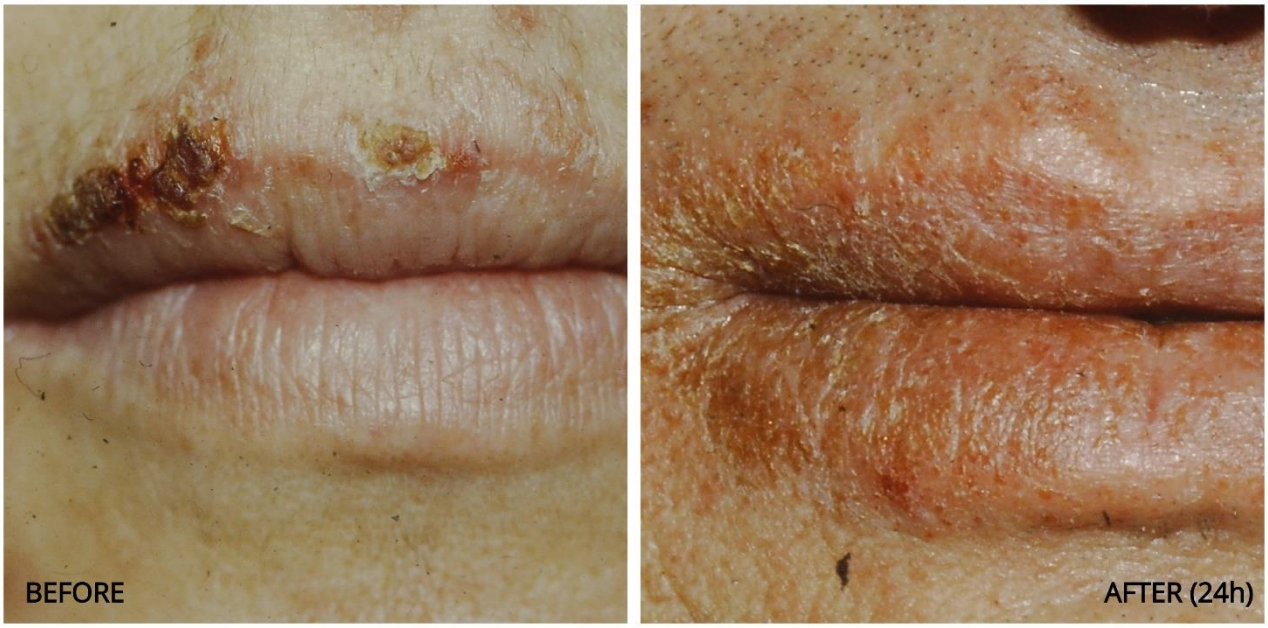

Fig 1:- Herpes simplex of the lips the very "first phase one-two trial" on myself. Regression of the lesion in 24 hours.

II. MATERIALS AND METHODS

Dose finding and safety issue: *C. parvum*, strain NCTC 10390 was cultured in the microbiology Dept, collected by centrifugation resuspended in saline at the concentration of $5x10^6$ CFU/ml and killed with phenol 1% at 70% washed and furtherly centrifuged, recovered and homogenously dispersed in 50 mg Hyaluronic acid IBSA (Hilow) at the same concentration.

I challenged one single intradermal inoculum of *C. parvum/ hyaluronic acid* during the bursting of a labial herpes simplex after sudden summer sun exposure with fever and pain. The intradermal injection was safe and painless, and the nodule generated by the inoculum was

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slightly tender and fixed, perceived for three days and then disappeared, being the surrounding skin reddened the first 12 hours; 18 hours later the lip infection amazingly started the regression process: the blisters became dried and brown the fever disappeared and the skin less edematous and painful.

I repeated the injection into the contralateral arm the day after while the restoration progress was accelerated and completed resolved in 3 days. I didn't feel any side effect due to these injections, so I planned to draw a detailed informed consent describing the procedure to be used in case of voluntary option of any patients affected by asymptomatic Herpes Zoster lesions or other cumbersome viral infection, with life impending risk or severe symptoms wishing to be submitted to the same therapy, on a compassionate spontaneous treatment plan.

In the following tables we report our clinical experience, with some slides describing cases and outcomes. The first table encloses 33 clinical cases both sexes (25 males and 8 females), aged between 5 and 75 years: 20 affected by Herpes zoster infection and 13 with drug resistant skin mycosis, treated along the period from February 1977 to June 1979, and other 19 patients (14 males and 5 females), aged between 9 and 97 years, recruited through the Second Opinion Medical Consulting Network, with Herpes Zoster and different common viral diseases, anecdotally treated along the last 10 years.

The selection criteria were:

A) Spontaneous request by the patient or his/her family of medical intervention for a better life quality support during a troublesome viral infection,
B) Urgent need of quick symptoms improvement or remission.

Exclusion criteria were multiple allergies, severe autoimmune diseases, decompensated cardiovascular diseases, unbalanced diabetes, cachexia or terminal cancer conditions. The patients were treated with single or multiple injections dependently by the virulence of the infection and symptomatic relieve rate in the first 12 hours after the inoculum.

In 3 cases of the second group, with bronchopulmonary inflammatory symptoms, we added inhalation powder of killed and freeze-dried *C. parvum* ($5x10^6$ CFU/ml) and Hyaluronic acid (50 mg), mixed together, in order to get an early better control of the respiratory distress locally activating the Broncho alveolar immune cells against the virus invasion and respiratory impairment.

Each patient underwent day by day medical visits to follow up the impact of *C. parvum* injection on the clinical course up to the infection remission.

III. RESULTS

Results are described in **tables 1 and 2**. The first encloses the very first group of patients challenged in the period 1977-1979, 21 affected by Herpes zoster and 12 with mycotic infections; the second group reports further treatments in the following years for Herpes zoster and other intercurrent virosis.

All the patients had quick remarkable benefit from the antiviral aspecific vaccination with killed *C. parvum* mixed into hyaluronic acid. In a very short time 36,48,72,96 hours dependently by the intensity of the clinical symptoms, and by the individual physical background. The procedure was generally safe without major side effects: some skin redness and itching over the inoculated area was observed in 15% of the cases, short lasting fever peak two hours after the injection in 25% of the non-Herpes zoster viral infections, slight cephalea in 10%; nausea and vomitus 2%. The skin eruptions of zoster infections and varicella started regression usually after 48 hours with vesicles and blister turning to brown crusts with contemporary improvement of pain. We report samples of aspecific *C.parvum* + hyaluronic acid immunization **(Figures 2-6)**. The compliance to the treatment was very high.

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TABLE 1: First group of c. parvum treated cases between 1977 and 1979

N.	Pat. name initial	Gender	Age	Type of Herpes viruses	Immunization schedule	Outcomes
#1	F.C.	M	5	Herpes Zoster Ophthalmicus	N° 5 injections for 6 days	Remission 5th day
#2	A.W.	M	50	Cervical dorsal herpes zoster	N°3 injections for 7 days	Optimal remission 3th day
#3	M.C.	F	75	Genital Herpes Zoster	N°5 injections for 7 days	Optimal remission 6th day
#4	V.M.	F	72	Popliteal Herpes zoster	N°3 injections for 4 days	Regression 48hours
#5	Z.H.	M	39	Scapular Herpes zoster	N°4 injections for 6 days	Remission 48hours
#6	B.G.	M	73	Herpes zoster on the face	N°4 injections for 7 days	Remission 8th day
#7	C.L.	M	18	Recurrence Oral Herpes	N°4 injections for 6 days	Healing, no symptoms for 1 year
#8	V.R.	F	24	Recurrence Oral Herpes	N°4 injections for 7 days	Remission, no recurrence for 3 years
#9	C.A.	M	52	Oral Herpes	N°4 injections for 7 days	Remission
#10	P.W.	F	46	Genital Herpes	N°4 injections for 7 days	Remission 6th day
#11	G.E.	M	61	Lumbar herpes	N°4 injections for 6 days	Remission
#12	V.P.	M	16	Herpes on the face	N°6 injections for 8 days	Remission 6th day
#13	G.V.	M	46	Recurrence Oral Herpes	N°4 injections for 7 days	Remission, no symptoms for 2 years
#14	L.E.	M	67	Thoracic herpes zoster	N°4 injections for 6 days	Remission
#15	M.R.	M	19	Nasal Herpes	N°5 injections for 6 days	Remission
#16	C.A.	M	64	Lumbar herpes Zoster	N°3 injections for 7 days	Remission 96hours
#17	S.D.	M	38	Aphtha	N°4 injections for 5 days	Remission
#18	C.S.	M	66	Oral Herpes	N°3 injections for 7 days	Remission 1 year
#19	G.F.	M	52	Oral Herpes	N°5 injections for 6 days	Remission, no recurrence
#20	M.F.	M	46	intertriginous dermatitis	N°4 injections for 10 days	Remission
#21	S.G.	M	33	Athlete's foot or tinea pedis	N°4 injections for 12 days	Remission
#22	G.E.	M	28	Candidiasis	N°4 injections for 10 days	Remission
#23	P.E.	F	67	Onychomycosis	N°5 injections for 7 days	Remission
#24	M.N.	M	51	Thrush	N°4 injections for 3 days	Remission (monotherapy)
#25	C.C.	M	39	Otomycosis	N°3 injections for 5 days	Remission, no recurrence after 1 year
#26	Z.E.	F	76	Genital mycosis	N°5 injections for 8 days	Remission , also after 1 year
#27	T.S.	M	42	Bacterial blepharitis	N°4 injections for 6 days	Remission (monotherapy)
#28	F.G	M	53	Dorsal mycosis	N°5 injections for 9 days	Remission
#29	C.A.	F	64	Mycoses on the breast	N°4 injections for 10 days	Remission
#30	L.A.	M	36	impetiginized atopic dermatitis	N°4 injections for 8 days	Remission
#31	S.L.	M	40	Genital mycosis	N°4 injections for 8 days	Remission
#32	M.S.	F	59	Candidiasis, Oral herpes	N°4 injections for 7 days	Remission
#33	C.U.	M	59	Scapular Herpes	N°4 injections for 6 days	Remission 3th day

Table 1:- First group of *C. parvum* treated cases between 1977 and 1979

TABLE N.2: Patients with different viruses infections treated with c. parvum from 2013 to 2019

N.	Date	Pat. name initial	Gender	Age	Diagnosis of infectious disease	Symptoms and Complications	Immunization schedule	Outcomes
#1	06.10.2015	A.S.	M	18	Mumps	Orchitis, pancreatitis, fever parotitis	N° 5 inject s.c each other day	Remission 10th day
#2	08.02.2016	B.P.	M	34	Varicella	Severe eruption, hyperthermia, itching, vomitus, nausea and dizziness	N°3 injections each day	Smartly improved 5th day
#3	11.04.2014	M.D.	M	12	Measles	Hyperthermia, cough, headache, fatigue, pleurisy	N°3 injections each day	Quick remission 6th day
#4	07.05.2017	C.C.	M	72	Herpes zoster	Lumboasciatic eruption, pain, and reduced motility	N°3 injections each day	Regression 5th day
#5	05.09.2013	M.M.	M	65	Herpes zoster	Face eyes neck, excruciating trigeminal pain, scotomas, and fever	N°3 injections each day	Improved at third day
#6	07.10.2016	M.L.	M	41	Herpes zoster	Groin, scrotum, penile perianal ulcerated vescicles pain	N°2 injections	Improved, remission
#7	08.08.2015	R.M.	F	63	Herpes zoster	Toraco abdominal wide eruption, fever, pain, and insomnia	N°2 injections	Improved at third day
#8	11.04.2017	C.C.	M	34	Cocksackie	Pleuritis, intrerstitial pneumonia, fever, colitis	N°3 injections each day plus powder inhalation twice daily for y6 days	Regression 5th day
#9	12.09.2018	B.S.	M	71	Influenza	Hyperthermia seizures, dizziness, cough	N°1 injection	Quick improvement, 3 days
#10	11.01.2017	M.S.	M	88	Influenza	BPCO, severe dyspnea, pleurisy, thoracic pain	N°4 injections daily and powder inahalations once aa day for 5 days	Remission 4th day
#11	14.02.2019	C.A.	F	93	Influenza	High fever, cardiac dilatation, reduced ejection fraction	N°2 injections each day and N°3 inhalations daily	Improved at third day
#12	16.04.2017	C.G.	F	97	Influenza	High fever, arthritis, legs oedema cough, vomitus, reflux	N°3 injections each day	Remission 4th day
#13	24.06.2015	M.S.	F	49	with displasia and inflamm	Endometritis, fever, pain, vaginal discharge	N°2 injections	Remission 3th day
#14	07.03.2013	R.P.	M	18	Measels	Fever, cough, hypertermia, absence, blurred vision	N°2 injections each day	remission 5 days
#15	31.01.2015	G.L.	F	9	Measles	Cephalea, fever, neck stiffness, eruption, itching	N°1 injection	Improved 2th day
#16	26.11.2014	M.C.	M	65	Varicella old age	Eruption, dysponea, fever, lung oedema	Diuretics + 2 injections each day pus inhalation once a day for 5 sessions	Remission 3th day
#17	30.09.2018	M.M.	M	36	Mumps	Severe pain, fever, mumps, scialoadenitis, oral aftae	N° 4 daily injections	Regression 5th day
#18	23.06.2016	G.R.	M	22	Viral tonsillitis	Hypertermia	N°1 single injection	Remission
#19	05.03.2019	Z.G.	M	58	HIV with stomatitis severe	Fever, pain, oral and lips inflammatory oedema, trisma	N°3 injections each day	Regression 4th day

Table 2: Patients with different viruses infections treated with *c. parvum* from 2013 to 2019

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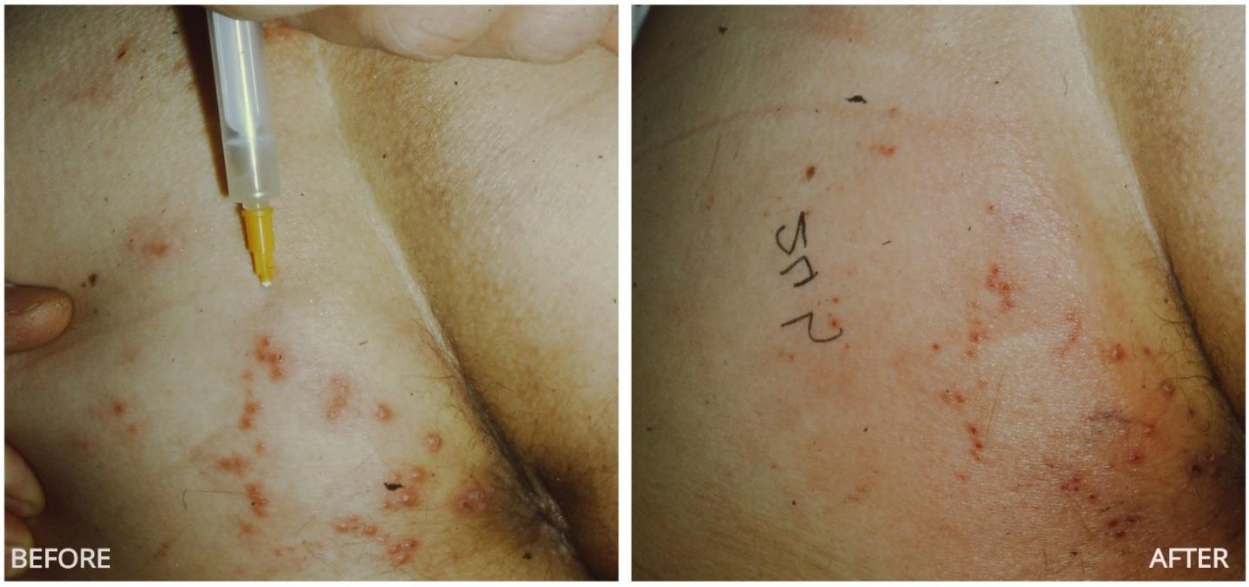

Fig 2: Genital H. zoster, subdermal injection. 24 hours later: regression of the vesicles

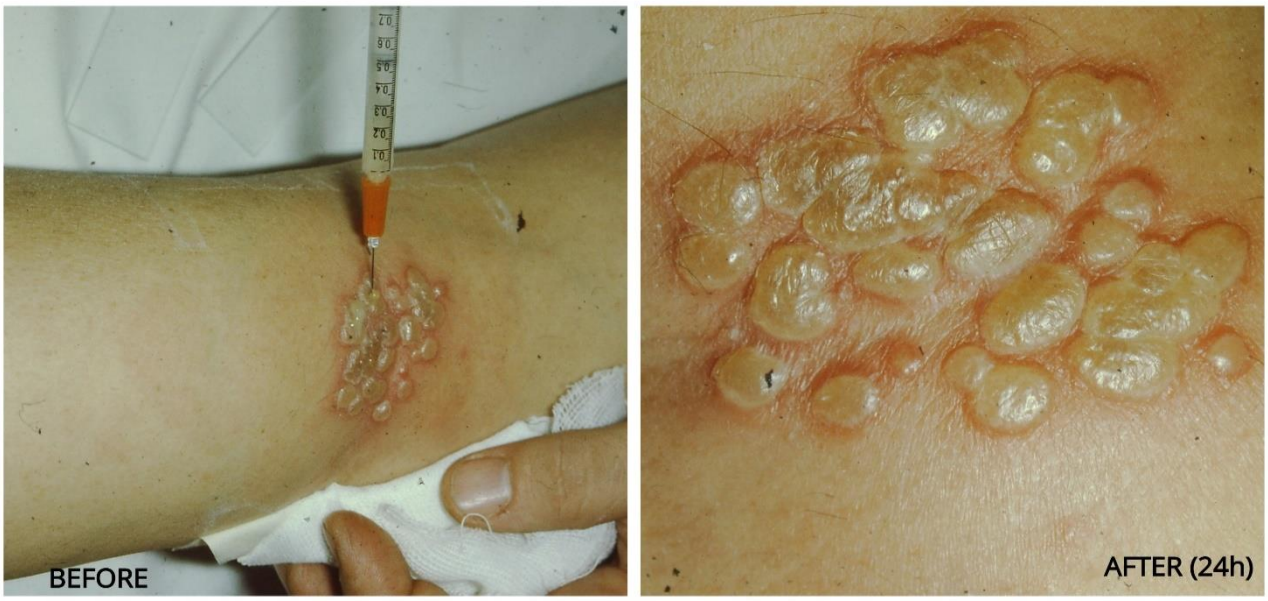

Fig 3: Lower leg H.zoster subdermal injection. 24 hours later the blisters are distended and start deflating turning into the crusting phase: patient's pain is relieved
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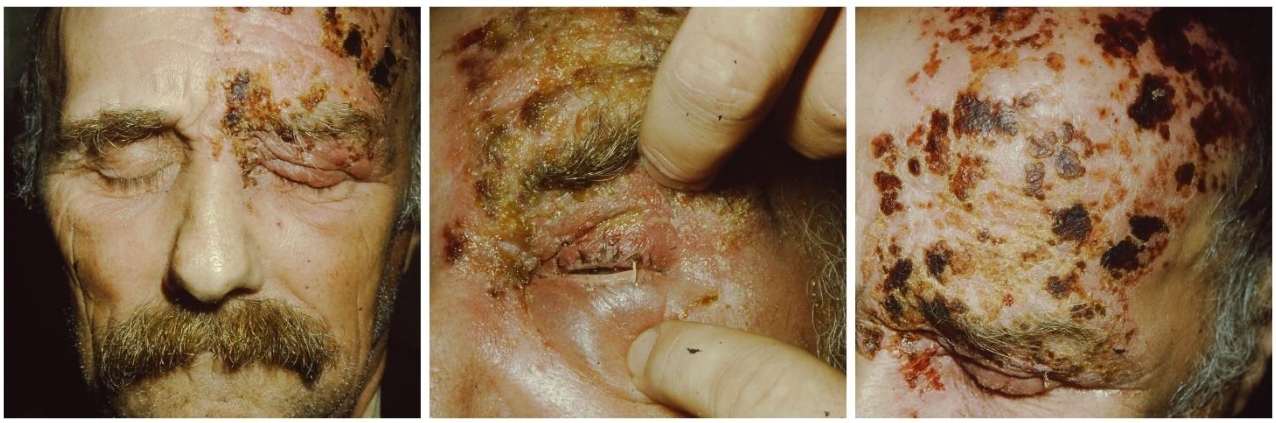

Fig 4: Temporo-facial H.zoster: Time 0, 24 hours later the exudating acute phase healing process is triggered.

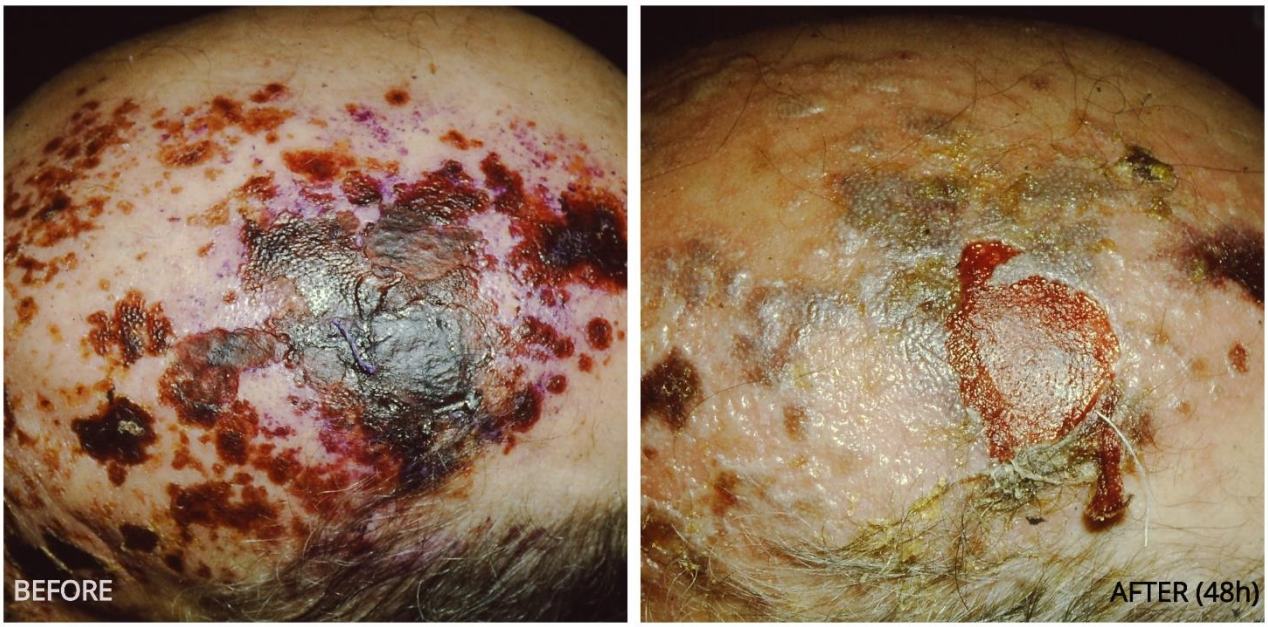

Fig 5: Galea capitis Herpes zoster pre and 48 hours post injection

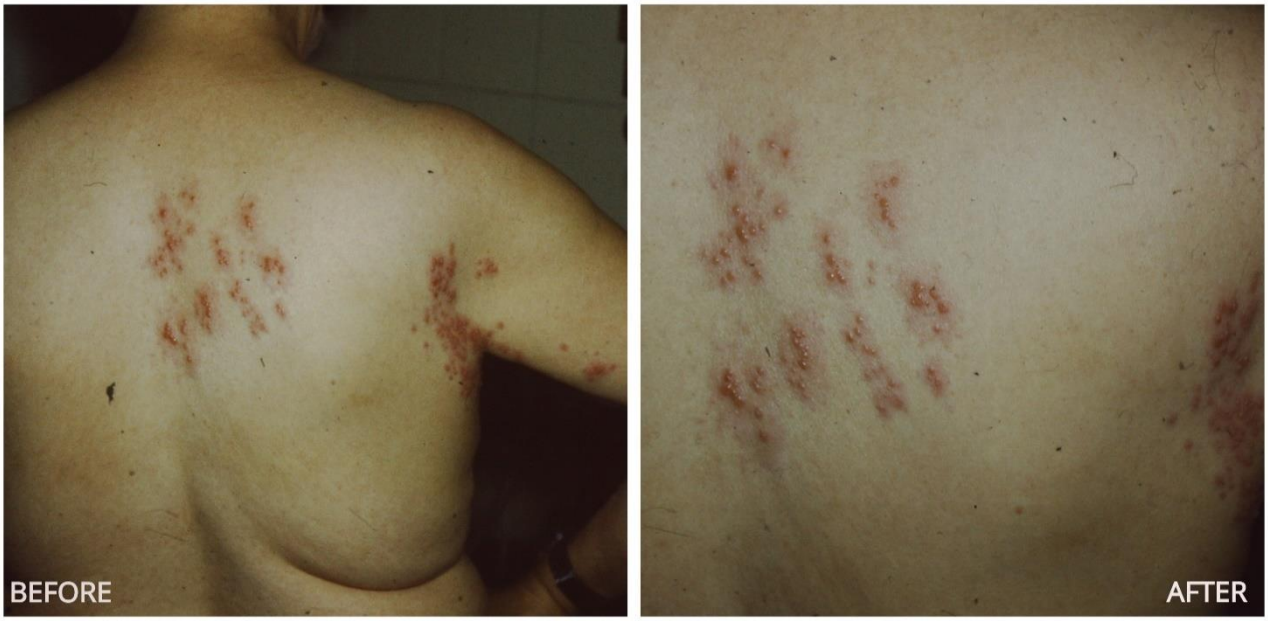

Fig 6: Scapulo axillary *H.zoster*: time 0 subdermal injection. 24 Hours post vaccination

IV. DISCUSSION

Our pilot trial reports a long-standing experience with killed *C. parvum* initially on zoster, and skin relapsing and resistant mycosis subsequently on some different common viral infections whose outcome was as well successfully achieved, quickly improving the symptoms and accelerating the remission. This therapeutic approach is clinically defined: "*non-specific antiviral–antimycotic immunotherapy*" quite an old procedure with many scientific contributions in the first 70 years of the past century.

Obviously, the question: *"What the reason to keep alive such an obsolete not tailored immunomodulation strategy in the third millennium where we target straightly the DNA and RNA to kill viruses and bacteria?"*

Furthermore: "*Why use a whole dead very old (but very stable !!) microbe as immunizing agent, and not rather it's active cell wall polysaccharidic-glycoproteic fraction, P40 that has been identified and extracted by Bizzini and cow since 1977?"*

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On the other side, we have an antiviral effective drugs battery available since 1974, whose cycloviran is the very first milestone against herpes strains; we fight proficiently also HIV and HCV infections, and last but not least we have also vaccines to fulfill the scenery of the cures: what more?

In my opinion aspecific vaccination with *C. parvum* is still useful to reduce the number of recurrent infections in regularly relapsing patients rising up the level of immunosurveillance accordingly with the following criteria:

- The time interval of relapses should be at least doubled, compared with the previous infections rate.
- The antibiotic administration ought to be substantially reduced (and this goal nowadays is very important due to widespread antibiotic resistance of pathogenic bacteria in the human and veterinary setting),
- The number of yearly relapsing infections should dramatically drop. Henocq, Bizzini, Ickovic were the pioneers of encouraging positive clinical studies on recurrent infections successfully treated with P40 *C. parvum* fraction, but unfortunately no more contributions with this aspecific vaccination strategy have been reported on PubMed in the subsequent years **[25-27].**

Another appealing indication of surrogate *C. parvum* **aspecific vaccination, in an epidemiological prevention perspective, are the sudden unexpected new virus epidemics, where we do not have yet either vaccines or specific antiviral Chemotherapies: Ebola, Sars, and corona are the recent outbursts of viral scourges provoking so much alarm and concerns in populations and Institutions.**

In these situations the policy to administer *C. parvum* **to risk people (old comorbid, sick patients, relatives, etc) and also to contagious individuals is expected to be very helpful in the epidemic control, shortening the course of the disease, reducing morbidity and mortality and preventing the spread of the infection.**

In the case of Covid-19 epidemy, a very positive experimental study of mice protection from viral hepatitis due to a specific coronavirus [12], hopefully opens the chance that *C. parvum* vaccination will help effectively to counteract, in emergency, this human impending rampant infection, while the world is waiting for the production, and diffusion of specific vaccine.

In this perspective, considering the respiratory infection route of coronavirus and it's more dangerous complication, the interstitial pneumonitis; **we adopted the *C. parvum* and hyaluronic acid*** ***(**hyaluronic acid, based on our studies preclinical studies, has antivirus properties itself, and is an excellent *C. parvum* delivery and release system**) powder inhalation as a further local delivery approach to counteract virus access into the lungs, and fight the subsequent expanding, and sometime lethal, pneumonitis.**

V. CONCLUSIONS

Our vaccine formula, reviewing the previously treated cases, has shown to be very safe, and displayed a very quick benefit on the symptoms and the time to viral infection remission. This remarkably fast clinical benefit, in the zoster infections compared with acyclovir administration resulted undoubtedly competitive and strong, relieving also postherpetic neuropathic pain and fatigue in the follow up; this not negligible benefit, generally speaking, has to be taken into account especially in older fragile sick patients: in fact shortening the overall illness duration, full recovery and wellness is reached in shorter time and with less complications in any viral infection.

As to the question whether p40 fraction or *C. parvum* in toto should be the most effective protocol choice, we reasonably suppose that a stronger and wider immune sensitization might be triggered by the whole bacterium rather than by one single fraction even if p40 has been proven the substantial cell wall component responsible of the immunological response; based on our results the structural complexity, and cellular components of the whole dead microbe, might make the difference in the macrophages recruitment and humoral engagement to maximize the immune response.

In clinical oncology we have the example of modified *Mycobacterium tuberculosis* (BCG = bacillus Calmette and Guerin) registered to treat surfaceal and *in situ* bladder cancer: it is a live attenuated (by several culture in growth medium), bacteria responsible of bovine T:B: (*Mycobacterium bovis*), that has lost virulence genes pathogenic for humans. The European urology association reports in 2013 no conclusive evidence of different effectiveness between the various adopted mycobacterium strains: the immune stimulating anticancer mechanism of this aspecific vaccine is basically similar to the *C. parvum* action and can be summarized accordingly with Fuge and Coworkers **[28].**

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Steps in BCG activity	Mediated by
1.Infection of urothelial and/or bladder cancer cells	Fibronectin
2. Induction of immune reaction	Cell types: granulocytes, T-helper cells, dendritic cells, and macrophages Immune molecules: MHC class I, CD4+, various cytokines including IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-17, TNF-α, and IFN- γ.
3. Induction of antitumor effects	Th1 cells (acquired immunity) via CD4+ T-cells and CD8+ cytotoxic T lymphocytes (driven by IL-2, TNF, IL-12, and IFN-γ)
	Th2-cell (innate immunity) through NK cells (driven by IL-4, IL-5, IL-6, and IL-10) Neutrophil recruitment (via IL-17 release) and macrophages.

Table 3: The mechanism of action of BCG is quite similar to that of C. parvum. Abbreviations: IL, interleukin; MHC, major histocompatibility complex; BCG, Bacillus Calmette–Guerin; NK, natural killer; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma.

Also for this whole microbe aspecific vaccine, in order to rule out some local or systemic toxicity, there have been attempts to replace it with some of its wall skeleton fragments but, due to their poor solubility and strong negative charge, the project has been abandoned.

More recently the pharmatechnology progress opened new perspectives via liposome incorporation or modification of the physical characteristics of the cell wall phragments, but clinical trials are still in progress.

Compared with the living attenuated BCG, and the possible systemic infection side effect, on the basis either of the literature review and of our direct experience, the dead *C. parvum* administration appears quite safe and manageable. The future trends of our investigations will be addressed to evaluate the possibility to enhance in vitro the antiviral *C. parvum* immune potential or to storage into the bacterial cell some virus-toxic molecules; actually we still support, in emergency, the *C.parvum* vaccination accordingly with its historical protocols.

- *Data Availability*

The clinical data used to support the findings of this study are included within the article.

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