Innate Immunity Stimulation During COVID-19 Pandemic: Challenge

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Abstract

AIM: We report an open spontaneous anecdotical retrospective survey of *Corynebacterium parvum* administration to 4000 fragile immune-depressed and multimorbid patients treated with a killed *C. parvum* strain to enhance the innate immunity integrating the adaptative immune response for a long standing antinfectious resistance.

METHODS: 4000 patients (1900 men and 2100 women) with mild, moderate or chronic disease, appealing to our Second Opinion Medical Consultation Network, signed an informed consent and were injected subcutaneously with *C.parvum*. The treatment was followed up at 6 months after therapy, filling the short form of the medical outcome health survey questionnaire (SF-36), directly by the patients or its parents and monitoring the health regularly via telemedicine (Skype, WhatsApp, mail, etc) or physician's visit.

RESULTS: The main efficacy endpoints, as assessed by the SF-36 questionnaire, are significant improvements in the mental and physical role functioning score ($p< 0.02$), in general health, in social role functioning ($p < 0.02$), vitality ($p < 0.03$), and a significant reduction in bodily pain ($p< 0.03$). There was a quick (48-72 hours) symptoms improvement and/or complete regression of the herpetic eruptions observed in 1000 affected patients and of herpetic neuralgia (reduced in 80% of cases), also full recovery or frequency reduction (30%) of recurrent cystitis and prostatitis in 120 affected patients, and last, but not least, a life quality improvement in 100 oncologic patients of overall 200 cases. A significant increase in the lymphocyte count ($p<0.01$), mainly Helper and Killer lymphocytes, was noted after 6 months by Parvulan injection vs. the baseline.

The asymptomatic SARS-CoV-2 patients, incidentally, enrolled in our survey, were tested at sixth months for antibodies against SARS-CoV-2 and 14 patients occurred high level of SARS-CoV-2 antibodies. The incubating Covid infections in the Parvulan injected patients even if rail and multi-morbid recovered in a short term (48-96 hours) and with benign clinical course, usually no need of further drugs administration except for the variants, which lasted on average one week and required some antipyretics, and low dose steroid for a few days.

CONCLUSIONS: Our results confirm that *C.parvum* is quite safe and effective to support immune-compromised patients when epidemic or pandemic events rise the life risk and any kind of infections and complications rate.

Further double-blind placebo evidence-based studies are urgently required, and our numerically substantial not sponsored spontaneous observation aims exclusively to promote further evidence based double blind institutional studies.

1. Introduction

The innate immunity and the adaptive immunity are the two milestones of human being's defence of survival, against pathogenic agents facing either single patient infection or epidemic/pandemic widespread infections (1-4).

The innate immunity is the quick answer of five phagocytizing cytotypes [namely: monocytes, macrophages, dendritic cells, Antigen-presenting cells (APCs) metamyelocytes plus killer lymphocytes] (5-7). They fight the noxious invading agents at the entrance sites (virus, bacteria, fungi, and protozoa) and scavenge the blood stream as well. In fact, the innate immune system uses pattern recognition receptors, including the Toll-Like Receptors (TLRs), CD209+, mannose receptor, and complement receptors, to help recognize and kill invading pathogens (8). Meanwhile, the adaptive immunity, through dendritic and T&B cells memory activation, is alerted and starts the antibodies production more slowly (9).

The clearance of viruses, bacteria and fungi with activation of interferon family genes is usually completed in 48-72 hours; the cross talk between T and B immunity is contemporarily started to synthetize targeted antibodies in 2-4 weeks, with a long memory against possible future relapses; obviously (10, 11). The synergy of the two arms of immunity is effectively integrated also in terms of balanced antibodies production and prevention of wrong autoimmune response (12, 13).

Corynebacterium Parvum (recently re-named *Cutibacterium acnes*) is a millenarian commensal of the human skin checking and balancing its microflora environment, whose immune modulating properties were discovered in the sixties, burying the killed bacterium into subcutis (14-16).

The very first clinical use of *C.parvum* as a drug (CORYPARV, by the International Wellcome Burroughs Company) was in the oncological setting, because of its direct anticancer properties (cancer tissue infiltration of lympho-monocytes and macrophages) with prolonged survival and better life quality (17-19).

During our oncological studies, we realized that some patients contemporarily affected by sudden viral infections, remitted the infectious symptoms in 2-4 days, and these serendipitous observations were by us followed up and extended along the years curing different common virus infections either in otherwise healthy, or in multimorbid sick people (8, 9, 17, 20-22).

Meanwhile preclinical microbiological and virological studies supported this anti infectious *C.Parvum* property, but the registration of Coryparv expired, and nobody else, except us, growing the original strain in the University Lab pursued anecdotally and without toxicity it's therapeutic use in viral, bacterial, and fungal, resistant infections.

During the impending pandemic in 2020, before the distribution of specific vaccines, aside the Government recommendations to stimulate the trained immunity repeating previous vaccinations (mumps varicella, TB, and influential) we remembered the previous *C.parvum* lesson and started primarily self-administration in a group of practicing physicians with Parvulan (Brazilian brand Extratos Alergenicos), the unique worldwide ongoing original registration (9, 23, 24).

Subsequently, having acquainted the benefits of the innate immune system by our blood exams, we achieved the authorization to extend the practice also on selected high-risk people, frail multimorbid immunocompromised patients with infectious diathesis mainly in oncology and geriatrics.

2. Materials And Methods

Our study is a spontaneous anectodical, observational, retrospective investigation involving every Italian region, namely Veneto, Piemonte, Lombardy and Emilia Romagna.

Patients.4000 patients (1900 men and 2100 women) with diagnosed mild, moderate, or severe diseases, aged 18-90 years, appealing to our Second Opinion Medical Consultation Network* between November 2020 and May 2021 were admitted to Parvulan injection **(Table 1, Fig.1)**.

“The Second Opinion Medical Network is a consultation referral web and outpatients Office System enclosing a wide panel of specialists, to whom any patient with whatever illness or syndrome inadequately faced by the diagnosis and therapy can apply for an individual clinical audit (25-28)

The clinical data of the recruited patients is described in **Table 2.**

Inclusion and exclusion criteria. The inclusion criteria were: -Patients complaining of chronic mild/moderate/severe bacterial and viral or fungal infections in the previous 6 months and seeking an effective and adequate therapy beyond the antibiotics. They were recruited among the following cohorts: -Cancer, -Primary, secondary, and iatrogenic immunosuppression, -Multiple comorbidities, including old and very old people.

Being the start-up of our prescription coincident with the pandemic phase of SARS-CoV-2 during 2020 to the first semester of 2021, we could not rule out the inclusion of symptomatic or asymptomatic COVID-19 infected patients, generally in sustainable clinical conditions and exclusively at very early symptoms arousal (max 2-3 days of incubation), with saturation index higher than 85% and good haemodynamic, and haematological parameters. The exclusion criteria included: -Hospitalized patients -Subjects with multiorgan failure-Autoimmune diseases, -Pregnant women; -Terminal cancer patients, -Cachexia, -Patients with severely compromised cardio-respiratory and renal insufficiency.

Two Office Physicians at the Second Opinion Medical Network facility monitored the group daily by phone, mail, skype, WhatsApp, or outpatients visit. The clinical follow-up and side effects to the drug treatment, were overviewed with monthly auditing in terms of safety, effectiveness, and compliance of subjects.

Clinical protocol of subcutaneous injection of Parvulan. Each patient signed an informed consent of spontaneous submission to the procedure that was shipped to the Italian Medicines Agency (AIFA), accomplishing the rule of Institutional control of a drug registered in a foreign nation (by ANVISA Brazil) outside of the European Medicines Agency (EMA), to be injected in full accordance with the registered drug leaflet.

The post injection treatment was followed up to 6 months, filling the pre/post short form of the medical outcome health survey questionnaire (SF-36), directly by the patients or its nurses/relatives. It measures health-related quality of life (QoL) in eight settings: vitality, general health perceptions, physical functioning, physical role functioning, emotional role functioning, social role functioning, bodily pain, and mental health. Each scale is scored using norm-based methods, with percentage scores ranging from 0% (lowest or worst response) to 100% (highest or best possible response) (29).

Parvulan preparation, dosage, and administration. 2,5 cc of the Parvulan ampoule content is mixed with 0,25 cc of 1% xylocaine (to do a painless injection) and 0,25 cc of low molecular weight (4000 Dalton) recombinant hyaluronic acid (commercially available in the Dermoaesthetics area) for promoting a hydrophilic environment around the injected core in order to enhance the recruiting and imprinting of chemotactically challenged cells.

Parvulan was injected once only, or rarely twice, or more based on medical judgement and disease severity; the injected surface was the forearm, lateral shoulder area, more rarely the upper external gluteus or lower abdominal quadrants **(Fig.2)**.

The patients were informed that the individual reaction to injection might cause in the first 24-48 hours some erythema or itchy nodules spontaneously resolving or counteracted by antihistaminic or anti-inflammatory creams; the reaction is quite similar to the tuberculin injection, but quite slighter and never ulcerating. Very rarely (due to the low bacteria concentration and the tailored formulation) some subfebrile or modest febrile reaction might happen in the 12 hours post-treatment, spontaneously remitting, usually without antipyretic requirement.

Statistical analysis. Statistical analysis was performed using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). All data are presented as mean ± standard deviation (SD) and were analyzed using two-way ANOVA. $p < 0.05$ was considered significant.

Table 1. Patient's clinical characteristics: Clinical characteristics (sex, age, weight) of enrolled patients are listed in this table, where No is the number of patients, SD: standard deviation; kg: kilograms.

No. of patients	4000
Male	1900
Female	2100
Mean age (SD), years	38,6
Mean weight, Kg	77,8
Drug dosage, mode of treatment	3-5 mL- subcutaneous injection individually, tailored by weight and pathology

Table 2: Clinical-pathologic background of the treated cohort. Considering the non-normal distribution, non-parametric statistics were used to compare the disease's population. All descriptive data were reported in percentages (%).

Medical condition	N patients	%
Viral infection (Herpes zoster, herpes simplex)	1000	25%
Virus-induced immunosuppression (multiple aetiology immune-depression)	2210	55,2%
Autoimmune disease (thyroiditis, arthritis, hypothyroidism, fibromyalgia, chronic asthenia, Lupus erythematosus-SLE)	300	7,5%
Cardiovascular (hypertension, vascular brain insufficiency)	10	0.25%
Oncology (breast cancer, prostate cancer)	200	5%
Urinary tract inflammation (recurrent cystitis and prostatitis, vaginal mycosis, candida and trichomonas vaginitis, dyspareunia)	120	3%
Old age/ multimorbidity/diabetes	40	1%
Healthy people (Doctors, Nurses, Teachers)	120	3 %

3. Results

All the patients enrolled were treated with Parvulan. The main efficacy endpoints, as assessed by the SF-36 questionnaire administered at baseline and 3 months after treatment, are: significant improvements in the mental and physical role functioning score ($p< 0.02$), in general health, in social role functioning ($p < 0.02$), vitality ($p < 0.03$), and a significant reduction in bodily pain ($p< 0.03$). Changes in role limitations ($p= 0.02$) or emotional state, with reduction of typical symptoms observed during this pandemic era, including anxiety, panic, depression, mood alteration were found **(Figure 3).**

Using structured telephone or telematic interviews (Mail, Skype, WhatsApp) in our investigation, we observed significant positive clinical outcomes in all cohort of patients, that we summarized in **Table 3**.

Quick improvement and complete regression of the herpetic eruption observed in 1000 (25%) enrolled patients; of neuralgia (80% of patients with herpes zoster), also a resolution or reduction of common urinary tract diseases, in particular recurrent cystitis and prostatitis (30% of patients), and last, but not least, a life quality improvement in 100 oncologic patients.

Table 3: Clinical outcome of the treatment in symptomatic patients. Effects of Parvulan injection on No of patients (%).

Symptoms Modulation	No. (%)*
Quick (48-72h) cutaneous herpetic eruption regression (thorax, head, neck, and genitals)	100%
Improvement of post-herpetic zoster (neuralgia)	
Regression of common cutaneous Herpes simplex (genital herpes and herpes labialis, stomatitis and mouth sore)	80%
Delayed relapse of resolution of urinary tract inflammation (recurrent cystitis and prostatitis, vaginal mycosis, candida and trichomonas vaginitis, dyspareunia)	30%
Life quality improvement of oncologic patients	2,5%
Reduction of common symptoms in autoimmune diseases such as fibromyalgia, arthritis, psoriasis, atopic dermatitis	10%

A significant increase in the lymphocyte count ($p<0.01$), mainly Helper and Killer lymphocytes, was noted after 6 months by Parvulan injection vs. the baseline. Relevant changes in neutrophil and eosinophil count were identified ($p>0.05$) **(Fig.4).** In addition, Parvulan treatment had no influence on all other values, such as haemoglobin (Hb), Alanine aminotransferase (ALT), aspartate aminotransferase (AST) level et al.

Levels of lymphocyte sub-populations were compared between before and after treatment, included CD3+ lymphocytes, T-helper cells (CD3+, CD4+), Suppressor T-cells (CD3+,CD8+) and Natural killer T-cells (CD16+,CD56+). CD3 **(Fig.5)**.

Table 4: Patients that occurred adverse events after Parvulan injection. Number (percentage) of patients with adverse events after treatment

	N (%)
Skin lump and soreness at the injection site (uncomplicated, plain resolution)	1920 patients (48%)
Cutaneous swelling	320 patients (8%)
Short term pain at the injection site	1480 patients (37%)
Injected upper arm soreness (short term spontaneous resolution)	320 patients (8%)
Skin rash around the injected area	960 patients (24%)
Fever, low grade in the first 8 hours, no antipyretics requirement	20 patients (0.5%)
Short term fatigue (Influential symptoms)	8 patients (0.2%)

The cutaneous reactions (rash, swelling) developed 24 to 72 hours after injection, and lasted two to seven days, the skin rash resolved in 24-48 hours, the skin soreness and lump lasted 7-10 days (1-2 months in few cases) **(Table 4) (Fig.A-D).**

The skin reactions either regressed spontaneously or were successfully treated with arnica, Flector Diclofenac gel or plaster, topic gentamycin.

The asymptomatic SARS-CoV-2 patients (3%), incidentally enrolled in our survey, were tested at sixth months for antibodies against SARS-CoV-2 and 14 (0,35%) patients occurred high level of SARS-CoV-2 antibodies.

The protection of healthy Parvulan injected individuals was very high. SARS CoV-2 infections in Parvulan injected patients were short term and with benign clinical course (low fever, low mild oropharingotracheobronchial symptoms, anosmia, dyspepsia, and bowel irritation) usually no need of further drugs administration except for the variants, which lasted on average a week and required some antipyretics, and low dose steroid for a few days.

The hospital admission rate was very low as well, no deaths and no intubation required.

As to the antiCovid-19 IgG IgM titres the wide range depends by the viral load and virulence met by the parvulan injected patients.

4. Discussion And Conclusion

Our study supports the concept that the killed *C.parvum* injected subcutaneously at the proper dosages effectively activates the innate immunity and offers several benefits especially along a pandemic emergency; in fact the brittle and multimorbid people, especially at old age, are exposed to several infectious risks contemporarily or meta chronically, and each relapse or new infection weakens more and more the healing power and vitality of the patient; Herpes simplex and Zoster and aphthous mouth ulcers, in example are sortie viruses that worsen very often the life quality of immunocompromised patients overlapping to previous infectious diseases or cancer or metabolic impairment; also recurrent urinary tract infections or mycotic vaginal discharges, or pharyngotonsillitis or tracheobronchial inflammation, added to the current air pollution, relapse very frequently in the sick febrile patients.

For this reason, the *C.parvum* administration might putatively be considered either in prevention or in therapy aside to the current standard treatments of the evidence based medicine.

This bacterium has unique aspecific antiviral properties, quickly counteracting the invasion of many viral strains, in experimental animals, human and veterinary pathology, but it has also successfully been challenged against bacteria, viruses and protozoa by direct phagocytosis and activation of the interferon family.

Furthermore, anecdotally and incidentally we supposed to have now retrospectively reached some proof of the concept that the una tantum treatment with *C.parvum* is effective to prevent SARS CoV-2 infection, and to neutralize the first stages (2-3 days) of the infectious symptoms of the original virus and it's variants, but further controlled studies are needed to better define this issue.

Resuming the history of our *C.parvum* endorsement in therapy, we were induced to re-discover and use it at the beginning of the pandemic when the COVID-19 vaccines were not yet available, and the National Health Committee recommended to enhance the trained immunity repeating some surrogate vaccination against i.e. tuberculosis , influential, Mumps etc…

Parvulan was at that time the unique Brazilian registration suitable for protecting our lives, and it's use on the very first group of doctors and nurses was intended, not as a trained immunity challenge, but, much more effectively as an INNATE IMMUNITY enhancement against any kind of infectious agent, incidentally, perhaps enclosing the SARS CoV-2 and its variants.

The life defense of the health caregivers practicing on the first line of emergency has been our primary concern of this choice: to raise an effective barrier against a high spectrum of whatsoever noxious agents, to reduce complexively the morbidity and mortality (the goal, retrospectively…. seems really to be reached…).

Out study confirms that, aside the Covid-19 vaccines, the *C.parvum* treatment ought not to be withdraw or dropped out.

In fact, the perfect integration between innate and adaptive immunity, accurately outlined by hundreds of scientific reports, strongly recommends to adequately blend the activation of both the arms in order to reach the more complete, protective and safe flock immunity.

The pre –post Parvulan hematological biochemical evaluation performed on our patients showed a general trend to increase the blood leukocytes, especially lymphocytes, neutrophiles and monocytes and (by immune phenotyping) of T helpers and natural killer.

As to the soluble immunity answers in our cohort, the SARS CoV-2 IgG and IgM antibodies concentration tested 2-3 months after the injection were quite different individual, ranges from 0 to very high levels (1720).

These findings can be explained by the fact that the very first commitment of innate immunity is to display a palisade of immune phagocyting cells across the infectious agents entry threshold and secondarily to alert the blood stream immune cells preventing the infection spread and the risk of sepsis; we have no routine tests available for the former submucosae population, but we have some for the latter; therefore the pre-post parvulan clinical history evaluation aside the hematological findings is mandatory for the final therapeutic judgement of effectiveness.

As to the observed wide range of IgG SARS CoV-2 antibodies, we reasonably suppose that they are not produced if the submucosal immune phagocytizing cells definitely prevent the virus entrance, but if some virions enter in a closer contact with Antigen-presenting cells (APCs) locally or in the blood stream, the adaptive immunity is furtherly triggered and modulated by the innate one.

A great number of our patients were affected by severe zoster infections, and very quickly answered to *C.Parvum* injection; even very old neuropathic complications improved or disappeared after the treatment; some time, after a single Parvulan injection, the Herpes relapsed (less virulent) and the injection had to be repeated twice or three times, with lower dosages in the follow up.

Other bacterial and fungal infections were successfully defeated as well **(Table 3)** and also some inflammatory skin diseases amazingly improved **(Figures 10-11)**, incidentally, many treated patients especially with chronic fatigue reported renewed brisky mental and physical energy observed usually after one week and lasting more than one month.

This note is out of the aim of our retrospective investigation, but some literature reports claim the effects of *C.parvum* especially on bone marrow and liver stem cells (30-33).

Regard the final comment about the side effects and toxicity warned by AIFA / Italy the 11 September 2021, the 50 years old oncological history of *C.parvum* leave no doubts about the great compatibility of this skin millenarian commensal bacterium with the human health and life; exceedingly high repeated

dosages in cancer patients, adults and kids never caused death or anaphylactic shock or multiorgan failures, or lung cytokine storms: only fever and chills easily controlled by the antipyretics (8, 17, 21, 22).

As to our standardized dosages, and una tantum schedules, we can bona fide confirm with exhaustive evidence the total absence of toxicity, complications, even in weak frail patients, that very often; on the contrary declared some mental and physical performance improvement; sometimes the skin injection produced itchy nodules (cytologically confirmed to be lumps of lympho-monocytes chemotactically involved), quite similar to the tuberculin skin reactions which disappeared gradually and almost spontaneously.

Concluding, our open anecdotical, spontaneous retrospective evaluation does not pretend to claim any other property of *C.parvum*, than the pure declarations of the Parvulan registration leaflet, but certainly the absolute safety of this drug is by our study definitely confirmed without any doubt or suspicion.

The activity against SARS CoV-2 and its variant were purely incidental findings during our practice, but they have to be taken into account, as an effective opportunity, to activate the innate and modulate the adaptive immunity at the same time. The innate immunity in fact is the very first aid to the survival law of every superior living species 3 million years before that evolution generated the second arm, the spontaneous or vaccinal antibody secretion by the adaptive immunity; the prominent role of the former, therefore, fully synergizes with the functions of the latter, regulating also some unbalanced responses of this last.

With Parvulan, we just intended to mitigate the dramatic selection of frail individuals inexorably observed during the pandemic in zootechnical facilities, or in elderly multimorbid human gender: the survival law ought, in fact for the humans to be somehow mitigated and our *C. parvum* fitted adequately with this role.

We really are not aware of what judgement, about our retrospective observation on 4000 treated cases will be sentenced by the Scientific Community; we are not keen to apologize for the many obvious bias that exclude ad interim our data from the evidence based arena; just we want to stress, that during a planetary emergency some reasonably safe and useful therapeutic weapon can profitably be exhumed and individually used, without conflicting with the Health Government diktats and fully accomplishing with the military vaccinations strategies or other new incoming tailored treatments.

Last, but not least, even if the fact that doctors preliminarily challenged on themselves the feasibility and benefits of parvulan injection, does not bring to our protocols any strength in terms of clinical methodology and statistical survey, notwithstanding, the prior involvement of health caregivers in the study would be an ethical concern worth of consideration.

Conclusively, we wish that our retrospective survey will focus the attention of clinicians and Companies (in a World that underscores and does not trust humble individual research highlighting mainly the big Pharma companies' discoveries) toward innate immunity potentiation, and integration together with the adaptive one.

The historical anti infectious and antiviral properties of *C.parvum* suggest it's safe and effective use to fortify fragile patients when epidemic or pandemic events rise the life risk and complications rate.

Further double-blind placebo evidence-based studies are urgently required, and our numerically substantial not sponsored observation aims exclusively to this goal.

Declarations

FUNDING

Funding information is not applicable / No funding was received.

CONFLICTS OF INTEREST

The Authors declare that there is no conflict of interest

DATA TRANSPARENCY

The authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained

DATA AVAILABILITY

The authors declare that data supporting the findings of this study are available within the article.

ETHICS APPROVAL

Approval was obtained from the local ethics committee Second Opinion Local Institutional Review Board (IRB), the number of Approval is 7/2021

AUTHORS CONTRIBUTION

The authors confirm contribution to the paper as follows: study conception and design: MV; data collection: AM, Proof, writing BP,

CONSENT TO PARTECIPATE

The participant has consented to the submission of the case report to the journal. Each Patient signed informed consent regarding publishing his data and photographs.

CONSENT FOR PUBLICATION

Each patient gave its consent for the publication of identifiable details, which can include photographs and/or case history and/or details within the text ("methods, results") to be published in the above Journal

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Figures

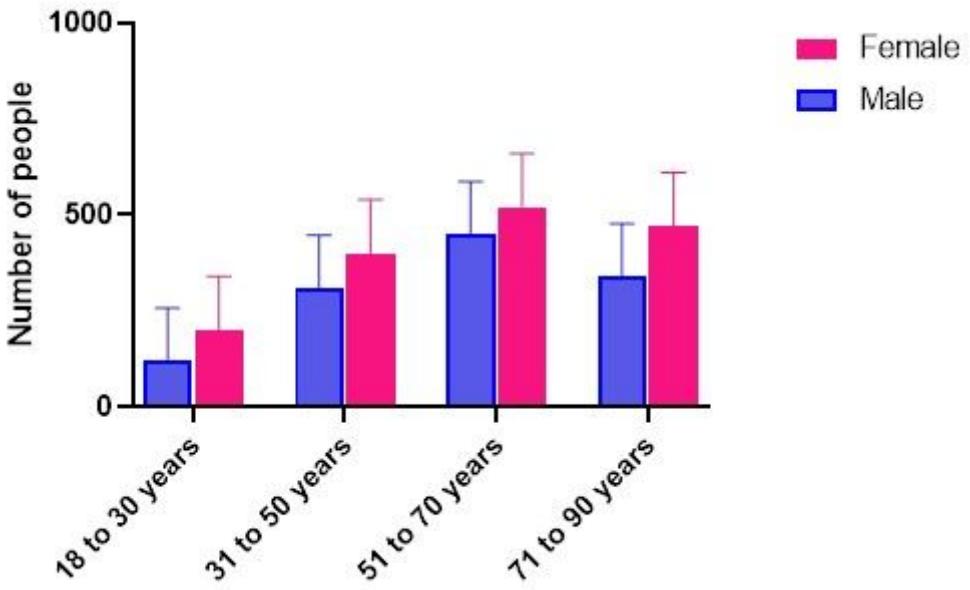

Figure 1

Distribution of population by age and sex. Bar graph shows numbers of males and females in 4-year age groups

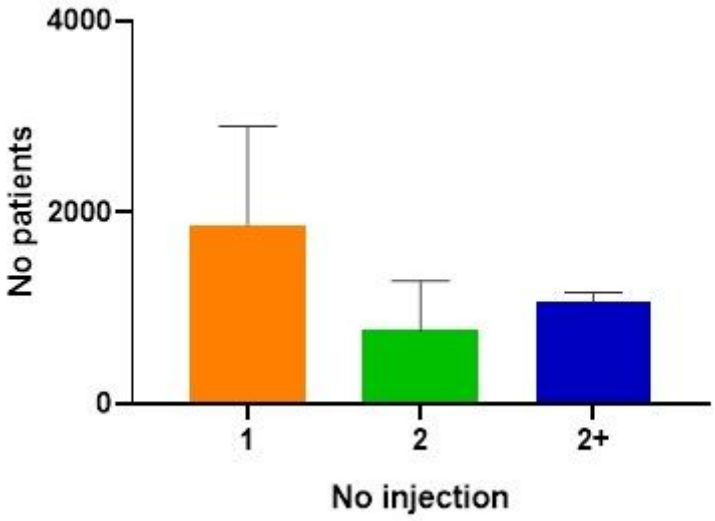

Figure 2

Graphic of No parvulan injection per patient. Frequencies of Parvulan injection (once only, or twice or more) in enrolled patients (n = 4000), based on medical judgement and disease severity.

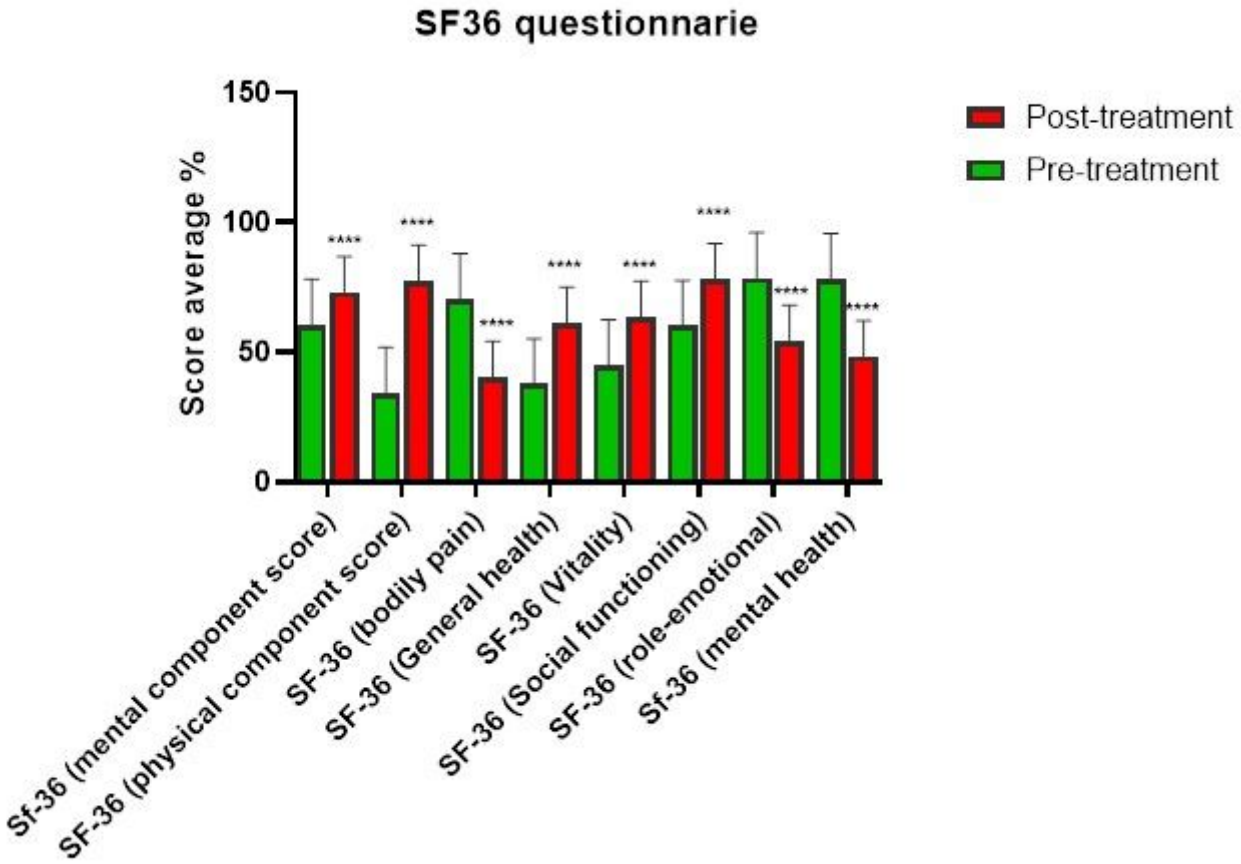

Figure 3

Graphical Representation of results SF36 questionnaire. Bar graphs showing the mean % SF-36 questionnaire results for the Pre-treatment (green graphs) and post-treatment (orange graphs) group. The post-Parvulan injection scores were already statistically better that those collected pre-treatment. Data are presented as mean ± standard deviation (SD). There are significant statistical differences between pre- and post-treatment. ****P<0.0001 pre vs. post-treatment

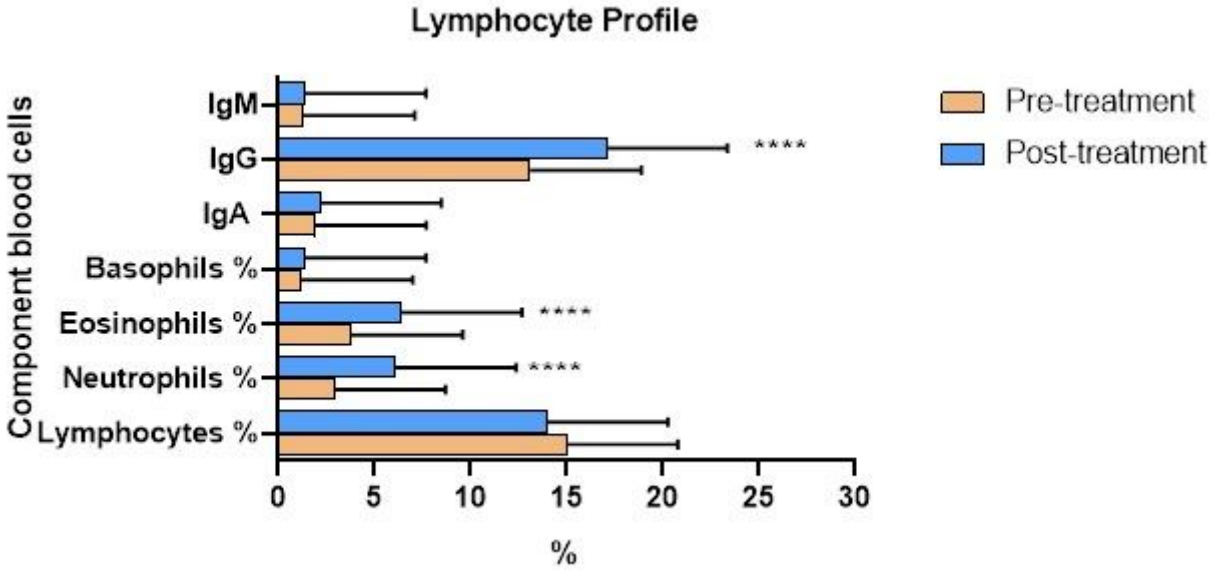

Figure 4

Graphical representation of lymphocytes component blood cells. The % number IgM, IgG, IgA, Basophils, Eosinophils, Neutrophils, Lymphocytes. There are significant differences in terms of IgG, Eosinophils and Neutrophils between pre- and post-treatment. ****P<0.0001 pre vs. post-treatment.

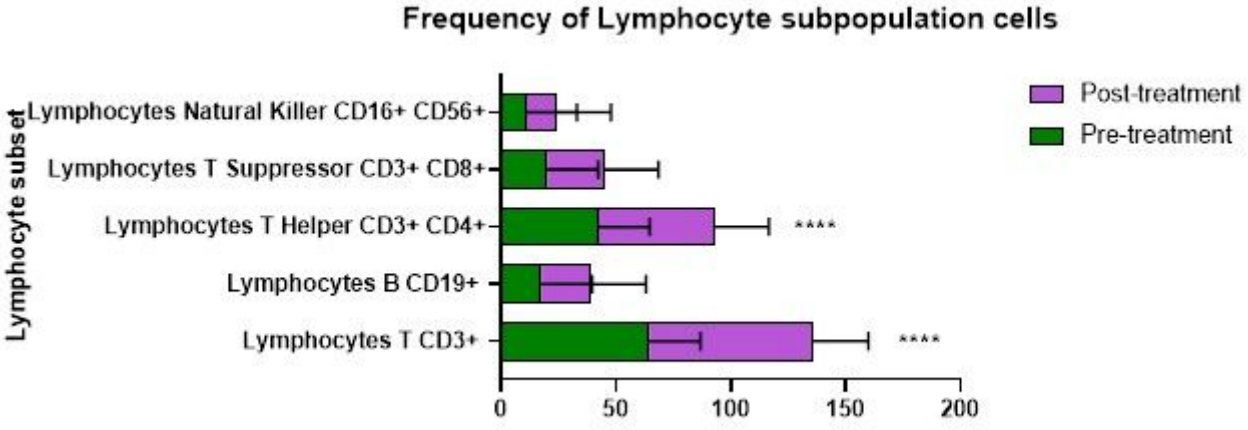

Figure 5

Graphical representation of lymphocyte subset before and after treatment. Data are presented as mean ± standard deviation (SD). Differences in CD3+ lymphocytes and T-helper cells CD3+, CD4+) were

considered statistically significant, relative to the pre-treatment group. ****P<0,0001 pre vs. post-treatment.

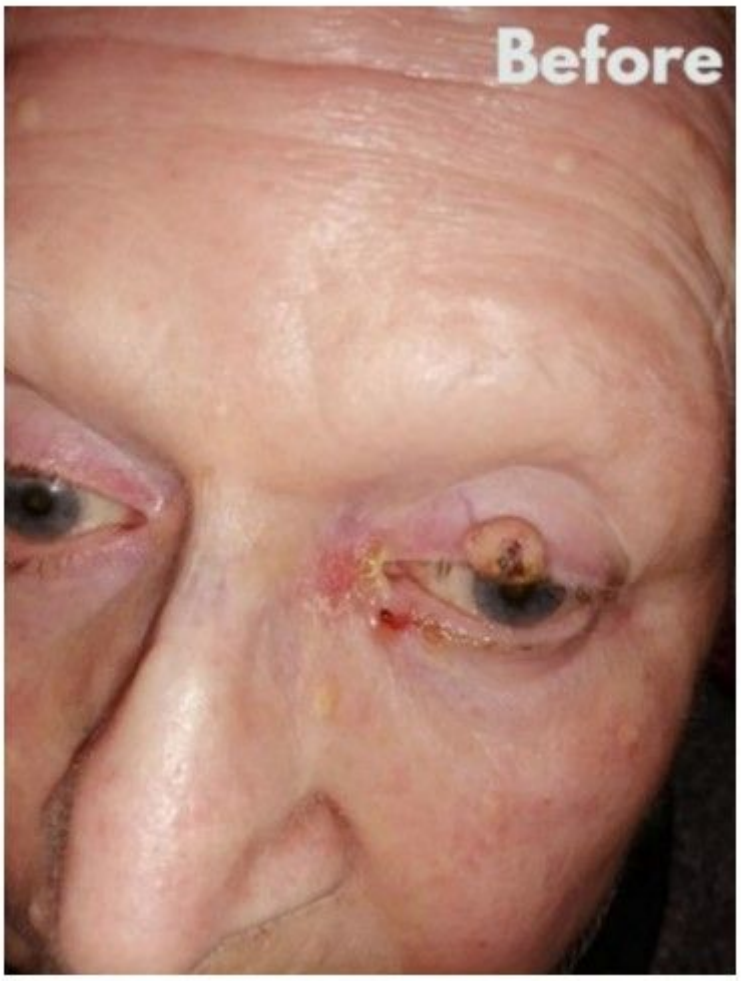

Figure 6

Photos of patient (AF, 80 years) with dacryocystitis, basalioma and blepharitis before Parvulan injection

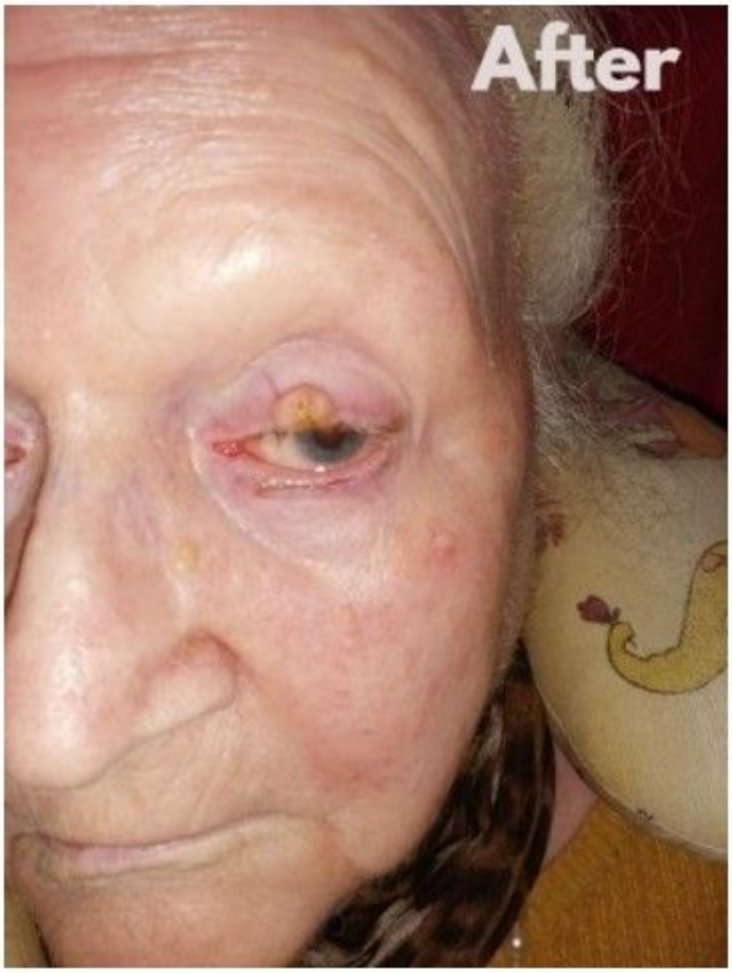

Figure 7

Photos of patient (AF, 80 years) with dacryocystitis, basalioma and blepharitis after Parvulan injection

Figure 8

A-D: Skin rash and skin lump in treated patients. A) Skin rash 2 days after Parvulan injection. Improvement of the lesion after 10 days with the use of Flector Diclofenac gel. B) Skin rash 1 day after treatment with spontaneous regression. C) Skin lump 72h after Parvulan injection, it regressed spontaneously after 3 weeks. D) Skin lump after 48 hours after treatment with spontaneous regression in 1 month