Annals of Case Reports
Schneider U, et al. Ann Case Rep: 7: 921.
www.doi.org/10.29011/2574-7754.100921
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research article

Post Covid19 Syndrome Treatment using Autologous Gold-Activated Serum: A Preliminary Clinical Study

Ulrich Schneider[1*], Peter Hollands[2], Martin Schicht[3], Friedrich Paulsen[3]

[1]CEO iRegMed GmbH, Gmund, Germany

[2]Freelance Consultant Clinical Scientist, Cambridge, UK

[3]Institute of Functional and Clinical Anatomy, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany

[*]**Corresponding author:** Ulrich Schneider, iRegMed Tegernsee, Center for Regenerative Medicine, Gmund am Tegernsee, Germany

Citation: Schneider U, Hollands P, Schicht M, Paulsen F (2022) Post Covid19 Syndrome Treatment using Autologous Gold-Activated Serum: A Preliminary Clinical Study. Ann Case Report 7: 921. DOI: 10.29011/2574-7754.100921

Received: 19 August 2022, **Accepted:** 23 August 2022, **Published:** 26 August 2022

Abstract

SARS-CoV-2 (Covid19) resulted in a global pandemic and an unprecedented public health crisis. Recent literature suggests the emergence of a novel syndrome known as Post Covid19 syndrome (Long Covid). This is a term used to describe a diverse set of symptoms that persist from 4 weeks from the onset of COVID-19 infection. Common symptoms include persistent breathlessness, fatigue and cough. Other symptoms reported include chest pain, palpitations, neurological and cognitive deficits, rashes, gastrointestinal dysfunction, retrosternal discomfort, and shortness of breath, poor memory, severe myalgia and an inability to return to work.

Methods: All patients (N=15) were treated by intravenous administration of gold-activated serum (Goldic®). Clinical symptoms were documented using a modified Halpin score. Re-evaluation of this score was done immediately after the treatment and after 4 and 12 weeks post-treatment. In 2 cases of acute respiratory distress syndrome (ARDS) follow-up CT scan was performed. The following antibodies were assessed in 8 patients: Anti-adrenergic and anti-muscarinic auto-antibody as well as plasma-gelsolin (pGSN) using ELISA.

Results: In all cases there was a significant clinical improvement following Goldic® treatment. The Halpin score decreased from 113 before the treatment to 53 immediately following the treatment and showed a further decrease after 4 weeks to 49 and to 36 after 3 months. The 8 patients who were assessed for auto-antibodies and showed pathologically elevated levels (mostly anti-muscarinic cholinergic receptor-1 and 2 antibodies) and a decreased pGSN level before the treatment. After the treatment most of the increased autoantibody levels returned to normal ranges. The pGSN level increased from 88.42 (+/- 6.03) to 96.42 (+/- 6.82) ng/mg protein immediately after the treatment.

Conclusion: This case study provides encouraging evidence for the use of Goldic® in patients diagnosed with "Post Covid19 syndrome". The gold-activated serum treatment appears to moderate the immune system and may be a new approach to treat a wide range of autoimmunological diseases. The measurement of autoantibodies and pGSN seems to be informative to monitor this treatment. Future comparative clinical studies have to be performed to investigate the full potential of this new approach in comparison with current treatments including higher patient numbers, a placebo group and a longer and more detailed follow-up.

Keywords: Post Covid19 Syndrome; COVID-19 Infection; Post- COVID-19 Syndrome; SARS-COV-2; Gold-Activated Serum Treatment; Autoantibodies; Plasma Gelsolin

Introduction

SARS-CoV-2 (Covid19) resulted in a global pandemic and an unprecedented public health crisis. It has infected more than 565 million people worldwide (WHO) [1]. The clinical features vary from a mild asymptomatic state which can be managed by the patient to a severe state with respiratory dysfunction, thrombotic complications and multiorgan failure requiring intensive care [2]. There are still many unknowns about the long-term progression of Covid19. For example, with pre-existing chronic respiratory, cardiac and some metabolic diseases seem to be at an increased risk of developing more serious disease. A new syndrome known as "Post Covid syndrome" or perhaps more correctly 'post-COVID-19 syndrome' has been described. Post-Covid-19 syndrome presents a wide range of symptoms. Post Covid-19 syndrome is highly heterogeneous, possibly reflecting the variability of definitions of this syndrome, the populations surveyed and the follow-up durations. 22-40% of Covid19 convalescent patients are expected to experience one or more symptoms of Post Covid19 syndrome [1,2]. The main signs and symptoms of Post Covid-19 syndrome are chest pain (up to 89%), fatigue (up to 65%), dyspnoea (up to 61%), cough and sputum production (up to 59%), cognitive and memory impairment (up to 57.1%), arthralgia (up to 54.7%), sleep disorders (up to 53%), myalgia (up to 50.6%), and functional impairment (up to 50%) [3]. There are no objective diagnostic criteria for Post Covid-19 syndrome. There is no consensus regarding algorithm of investigation, and no evidence-based interventions [4]. Some guidelines or recommendations for diagnosis and management of Post Covid-19 syndrome have been published, including those issued by the National Institute for Health and Care Excellence (NICE) published in December 2020 [5]. Despite this, there are still significant gaps regarding pathogenesis, incidence, potential risk factors, diagnosis, management and long-term outcomes of Post Covid-19 syndrome. There are currently no specific diagnostic markers for Post Covid-19 syndrome. Some workers have shown that there are elevated antibodies against ß2 adrenergic receptors (ß2) and muscarinic M3 and M4 acetylcholine receptors (M3/M4) in Post Covid-19 syndrome patients [6-8]. Antibodies to ß2 and M3 receptors have been reported in various other diseases including dilatative cardiomyopathy, postural tachycardia, regional pain syndrome, Alzheimer's disease, Sjoegren's syndrome, asthma and others [9]. This makes the diagnostic use of these markers unhelpful in Post Covid-19 syndrome. The use of gold-activated autologous serum (Goldic) is an innovative procedure to treat chronic inflammatory and degenerative diseases. This procedure is used mostly in musculoskeletal diseases such as osteoarthritis, tendinosis and muscle injuries [10]. In systemic diseases gold-activated autologous serum has been administered intravenously to address the overall disease, possibly altering the disease environment inside the body and harnessing the immunomodulatory/ immune systems anti-inflammatory role in regeneration [11]. In this study we investigate the outcome of intravenous gold-activated autologous serum treatment in patients with Post Covid-19 syndrome.

Materials and methods

Study protocol

The objective of this study was to evaluate the outcome of intravenous GOLDIC® treatment in patients with Post Covid-19 syndrome. This was an observational study carried out as a prospective case group study. All patients had been previously pre-treated unsuccessfully with various conventional treatments for Post Covid-19 syndrome before taking part in this study. All patients gave their written informed consent to take part in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Guidance for Good Clinical Practice.

Patients

Patients were diagnosed at the outpatient clinic for regenerative medicine (iRegMed) Gmund/Tegernsee in 2021. We used the current clinical guidelines for healthcare professionals who are treating patients following acute SARS-CoV-2 infection. The patient selection for the clinical study focussed on those patients who had not fully recovered during 12 weeks from the initial diagnosis of acute Covid-19. This is the definition of Post Covid19 syndrome [9] and it excludes other diseases which may cause similar symptoms. Further exclusion criteria were ≤18 years of age, or if participation in the study was inappropriate due to dementia,

learning disability, or other cognitive or communication impairment.

Treatment

For the gold-activated serum therapy, either 4 (in the first 6 patients) or 8 x 10 mL of blood (in the other 9 patients) was collected using Goldic® BTS syringes (Arthrogen GmbH, Gmund, Germany) at the time of initiating the therapy. All syringes were incubated at 37 °C (dry incubator) for 24 hours. Addition of anticlotting agent is not required as even if clot forms, it does not impact separating the cells and creation of the activated serum. After the incubation process, the tubes were centrifuged at 4000 rpm (2250g) for ten minutes. Then supernatant activated serum was collected and filtered through a 0.22-µM syringe tip filter (Sterifix, Braun, Melsungen, Germany), and was then used for immediate intravenous injection or stored at -20°C for later use. All patients received intravenous injections of approximately 3 mL. Goldic® serum was injected intravenously every three to six days under aseptic technique with a 22G needle.

Assessment of symptoms by modified Halpin-score

The presence and severity of symptoms were assessed:

- before onset of the disease,
- at the time of maximum symptoms
- before the treatment,
- directly after the treatment
- 4 and 12 weeks after the treatment.

The clinical symptoms were documented using a modified questionnaire developed by Halpin et al. [13]. Symptoms were classified according to a scale (0: no symptoms up to 9: very severe symptoms).

Assessment of Autoantibodies

Autoantibodies against AT1R, ETAR, α-1-adrenergic, α-2-adrenergic, β-1-adrenergic, β-2-adrenergic and muscarinic cholinergic receptor 1-5 were determined by using CellTrend GmbH (Luckenwalde/Germany) analytical ELISA technology. Pre- and post-treatment samples were analysed in the same assay run. The pre- and post-treatment samples were stored at -80°C before analysis. Elevated antibodies were defined as being higher than the 90% percentile of a healthy control group [7].

Assessment of plasma Gelsolin (pGSN)

The measurement of pGSN in the serum of the patients was carried out using a sandwich enzyme-linked immunosorbent assay SEA372Hu ELISA Kit for Gelsolin from Cloudclone Corp., Wuhan, China (distributed by Hölzel-Diagnostika GmbH, Köln, Germany) according to the given protocol. Serum was diluted to fit into the ELISA range and subtracted out afterwards. In addition, the total amount of serum protein was measured by Bradford assay to normalise the results after performing the ELISA.

Statistical analysis

Statistical data analyses of the Halpin score were done using the software Sigma Stat 6.0. Nonparametric statistical methods were used. Continuous variables were expressed as median and interquartile range (IQR). Univariate comparisons of two independent groups were carried out using the Mann-Whitney-U test or Fisher's exact test, comparisons of two dependent groups were done using the Wilcoxon matched-pairs signed-rank test. A two-tailed p-value of <0.05 was considered statistically significant. The analysis of the autoantibody and the pGSN measurement was done by descriptive methods based on the limited number of patients in the clinical study.

Results

Patient characteristics

This preliminary clinical study took place using 15 volunteer individuals, who were diagnosed with COVID-19. All patients had a positive Covid-19 PCR-test (nasopharyngeal sample) in their history before they developed Post Covid-19 syndrome symptoms. They initially presented with fever, cough, myalgia, anosmia and various rashes. All patients were instructed to self-quarantine at home and received supportive care. One patient was treated in an intensive care unit for 6 weeks. The data from this patient need separate consideration as the medical history is very different. Despite the initial efforts of the patients, they continued to experience persistent symptoms of fatigue, lethargy, intermittent dizziness, and tachycardia. Patients also experienced chest tightness, and persistent dyspnoea. The patients had no other significant medical history (apart from the patient who spent 6 weeks in ITU. Patients underwent a number of investigations, including blood tests, ECG and chest X-rays/CT.

The Post Covid-19 syndrome symptoms of the patients were so severe that they were unable to resume their work. Furthermore, the patients experienced a number of multifaceted cognitive symptoms including reduction in concentration, poor memory, "non-specific head buzzing", worsening anxiety, and 'brain fog'. Musculoskeletal symptoms included restless legs, non-specific paraesthesia across their hands and feet, and generalised body ache. All patients were reviewed by rheumatology, neurology, cardiology and pulmonary specialists for their existing Covid19 symptoms. Disease severity was assessed by a specially designed questionnaire for COVID-19 infections representing specific symptoms and impact on daily life. EQ' 5D‐5L is also evaluated in this score [13]. The CT-scan of the thorax was normal in 11 patients, four patients showed severe ARDS changes with marked infiltration in both lungs. The preliminary clinical study there included 15 patients with diverse arrays of symptom presentation. Most commonly persistent breathlessness was found, fatigue and cough (n=13). Other symptoms noted were chest pain, palpitations, neurological symptoms, rashes, gastrointestinal dysfunction and cognitive blunting (N=15). The baseline demographics and characteristics of these 15 patients are shown in Table 1. The average age of the patients was 43.2 years (SD 17.4), the average BMI (kg/m2) was 27 (SD 4.2). Most of the patients (n=12) were female, 3 were male. The duration of symptoms varied between 3 and 18 months (Ø 6.1). Six patients received 4 gold-activated serum injections, nine patients received 8 intravenous injections.

Patient	Age	Gender	Duration of symptoms (Months)	Number of Goldic injections	Pre-treatments
1	47	F	6	4	PT, ET,S,BB,AI
2	63	F	3	4	PT, ET,S,BB,AI
3	57	F	7	4	PT, ET
4	60	F	6	4	PT, ET,S,AH
5	23	F	7	4	BB
6	34	F	4	4	CBT
7	56	F	3	8	CBT
8	66	M	18	8	PT, ET,S,BB,AI
9	55	F	8	8	ET, PT
10	62	F	3	8	AI, PT, S
11	23	M	5	8	BB
12	25	F	6	8	PT,S
13	31	F	5	6	PT, ET,S,BB
14	22	F	6	8	PT
15	24	M	5	8	PT, ET,AH

Table 1: Baseline demographics and characteristics of the treated patients, previous treatments included; PT= physiotherapy, ET= ergotherapy, S=steroids, AI=anti-inflammatory drugs, BB=beta blocker, OT=Ozone therapy, HB=hyperbaric oxygen therapy, CBT=cognitive behavioural therapy, PT=psychotherapy, AH_Antihistamine, m=month, F=female, M=male.

Analysis of the modified Halpin-score showed that all patients had no or minimal limitations prior to COVID-19 infection (see Figure 1). At the time of infection, the mean score was at 102 points and showed no improvement in symptoms over time (T2 and T3) (see Figures 1 and 2). In all cases, clinical improvement was noted immediately after the treatment (T3). Further improvement was demonstrated after 4 and 12 weeks (T4 and T5).

The analysis of the subgroups fatigue and general health showed similar results compared to the global modified Halpin score with a significant improvement immediately after the treatment (T3 vs T4, $P<0.005$) and a further decrease of the score until the 3 month follow-up (Figure 3).

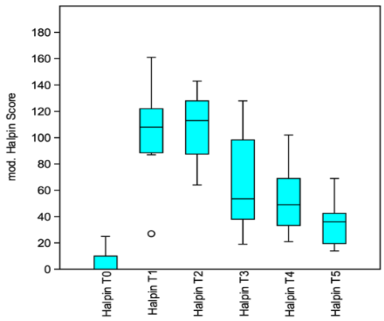

Figure 1: Modified Halpin-score (median and IQD) for baseline (before infection), during infection with SARS-Cov-2 (T1-2), after treatment (T3), 4 weeks after treatment (T4) and 12 weeks after treatment with intravenous gold-activated serum injections (T5).

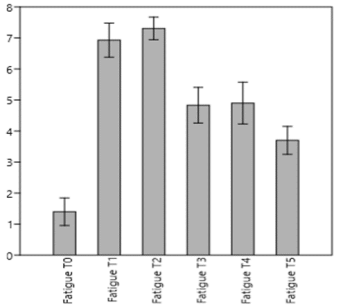

Figure 2: Demonstration of fatigue using Modified Halpin-score (median and IQD) for baseline (before infection), during infection with SARS-Cov-2 (T1-2), after treatment (T3), 4 weeks after treatment (T4) and 12 weeks after treatment with intravenous gold-activated serum injections (T5).

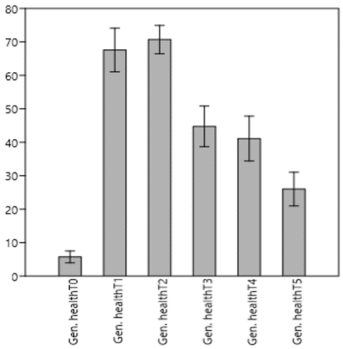

Figure 3: Calculation of general health situation using Modified Halpin-score (median and IQD) for baseline (before infection), during infection with SARS-Cov-2 (T1-2), after treatment (T3), 4 weeks after treatment (T4) and 12 weeks after treatment with intravenous gold-activated serum injections (T5).

The radiological investigation of the lung CT of one patient before and 3 months after the treatment showed a remarkable improvement (Figure 4). The initial pulmonary infiltrations in all parts of both lungs disappeared completely without any signs of fibrosis or scar tissue formation.

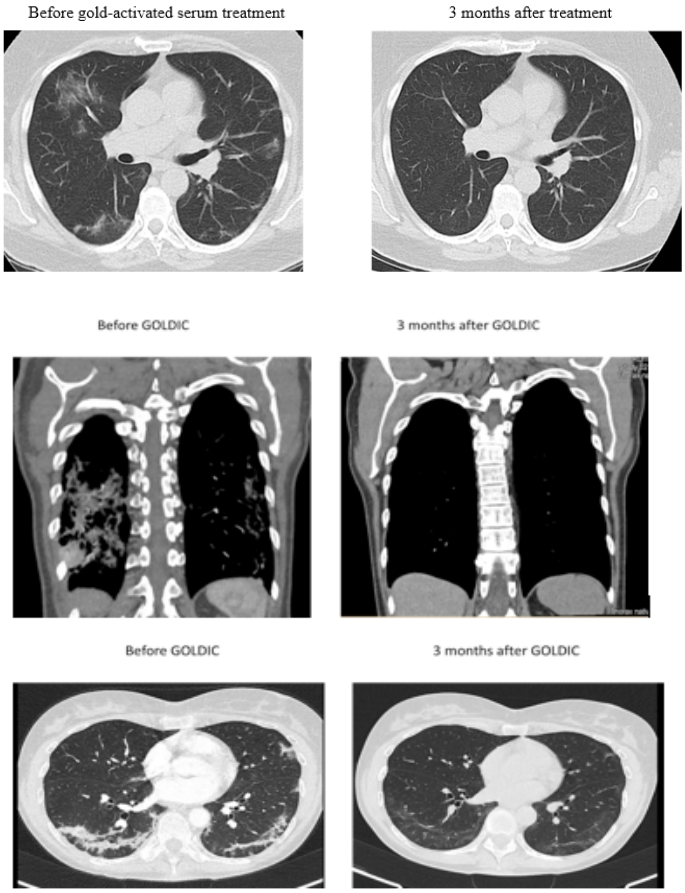

Figure 4a: Radiological documentation of a "Long-Covid" patient before and 3 months after treatment with gold-activated serum documented by CT-scan. The infiltration in both lungs disappeared completely. **4b:** Radiological documentation of another "Long-Covid" patient before and 3 months after treatment with gold-activated serum documented by CT-scan. The post infective destruction mostly in the right lung was regenerated after the treatment.

8 patients were screened for auto-antibodies and showed pathologically elevated levels before treatment (mostly anti-muscarinic cholinergic receptor-1 and 2 antibodies).

After treatment, most of the increased autoantibody levels returned to the normal ranges (Figure 5,6). The measurement of plasma gelsolin before (T0) and after the treatment (T1) showed an increase from 88.42 (+/- 6.03) to 96.42 ng/mg protein (+/- 6.82 ng/mg). No side effects or adverse events were detected during the study.

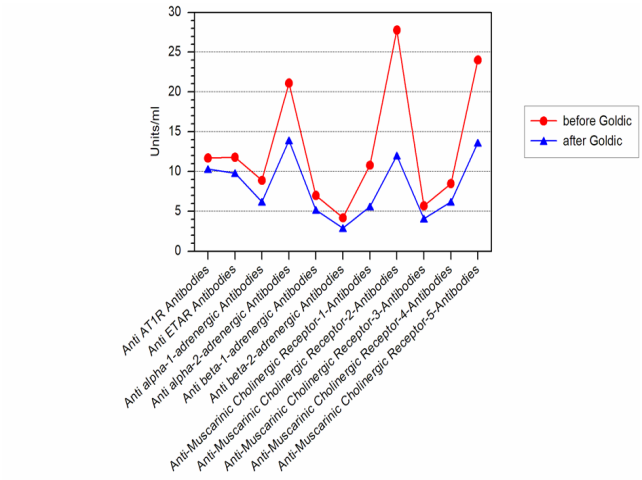

Figure 5: Demonstration of the measured autoantibodies in a typical Post Covid19 syndrome patient before and right after the treatment. The treatment showed different levels of improvement in the various autoantibodies.

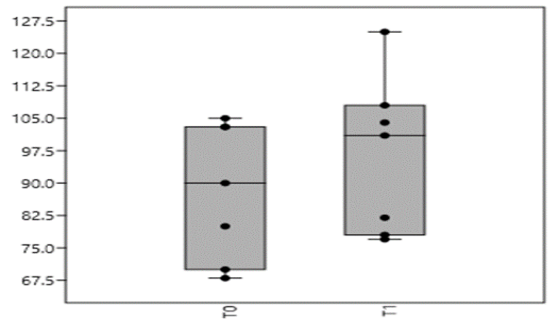

Figure 6: Demonstration of the measured pGSN levels before the treatment (T0) and immediately after the treatment (T1). The pGSN level was clearly elevated within the treatment.

Discussion

Post Covid-19 syndrome is a complex syndrome that describes the long-term residual effects of the acute COVID-19 infection [14]. Millions of patients worldwide experienced "mild" COVID-19 symptoms not requiring hospital admission. Despite this a large proportion are suffering from Post Covid-19 syndrome. Post Covid-19 syndrome was difficult to describe during the start of the pandemic but it has since become an enormous challenge for clinicians and the healthcare systems on a global scale. Post COVID-19 syndrome is defined as the signs and symptoms that develop during or after a COVID-19 infection. The symptoms may continue for more than 12 weeks post-infection and cannot be explained by an alternative diagnosis. The symptoms of Post COVID-19 syndrome are systemic and may fluctuate over time. Post Covid-19 syndrome-19 may occur in both patients with symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). Medical consultations should be offered to patients who are concerned about persistent symptoms lasting more than 4 weeks from the onset of acute COVID-19 [9]. This is particularly important in vulnerable groups but also in the general population. Investigations should be offered to rule out acute or life-threatening differentials (as in normal practice) in order to ensure the correct diagnosis of Post Covid-19 syndrome. These investigations should include blood tests-full blood count, liver and kidney function tests, CRP, ferritin, BNP, and thyroid function tests [14]. One of the challenging clinical apsects of Post Covid19 syndrome is the wide range of symptom presentation [14]. Mandal et al. [15] showed that patients most commonly present with persistent breathlessness, fatigue and cough. The patients in the Mandel et al. study [15] showed a 30% elevated D-dimer and 9.5% had a raised CRP up to 90 days after discharge. Other symptoms noted were chest pain, palpitations, neurological symptoms, rashes, gastrointestinal dysfunction and cognitive blunting. This wide variation in presentation contributes to a possible degree of diagnostic uncertainty, making the clinical management equally challenging. Symptom-orientated treatments may be useful in some patients suffering from post Covid-19 syndrome. At present there is no disease specific treatment avaiable. The use of gold compounds therapeutically has a long history, especially in the treatment of tuberculosis and rheumatoid arthritis, but there was always a problem with toxicity which has resulted in a decline in the use of gold compounds to the present day [16,17]. The introduction of GOLDIC® technology has enabled the benefits of gold compound therapy without the associated toxic side effects.

When using GOLDIC® technology no gold compounds are administered to the patient [10]. In previous studies, the GOLDIC® process increased plasma-Gelsolin (pGSN) levels and this may be key to the beneficial effects seen in the patients in this study [10,11]. It is known that free, or extracellular actin, can decrease the activity of macrophages and therefore enable infections to progress with greater speed and severity [19]. In addition it is known that pGSN is able to bind and cleave actin and therefore reverse this effect. It has been shown that a virus induced actin expression is increased when pGSN levels are low and that viral vesicular egress depends on pGSN function [20]. Perhaps the most interesting observation is the absence of viral infections following a GOLDIC® treatment, which was observed in a previous study [18]. This may be explained by the antiviral effects of p-Gelsolin (pGSN) which is upregulated during the incubation with Goldic®. A normal level of pGSN has frequently been reported in the literature to show a range of beneficial effects including reducing brain inflammation and apoptotic signalling in mice that had undergone thermal injury [21]. The use of Goldic® in a clinical setting may, following appropriate clinical trials, be an important intervention in patients who have undergone thermal shock, trauma to the CNS and cerebrovascular accident [22] and low pGSN can be a sign of poor prognosis in patients who have undergone ischaemic stroke and endovascular thrombectomy [23]. It has also been proposed that enhanced pGSN levels can protect against oxidative stress and may enhance wound healing [24]. This may be beneficial in overall general health. It is also proposed that low pGSN may result in more severe clinical outcomes in patients suffering from pneumonia [25]. The observations about the importance of pGSN in various pathologies suggest a possible wide range of applications of the Goldic® technology in routine clinical practice.

In addition to the therapeutic applications of pGSN, this protein has also proven to be a possible marker in Covid diagnostics. Numerous studies have confirmed this observation [27-29]. The intravenous administration of gold induced cytokines using GOLDIC® has shown impressive clinical efficacy overall with a very small incidence of side effects [18]. The side effects which have been observed were transient fatigue and peripheral irritations to the skin consisting of slight erythema at the intravenous injection site. Both effects may have been a physiological reaction of the body to the GOLDIC® activated serum or a simple common injection site reaction seen in some intravenous infusions. There is now increasing evidence that a great variety of autoantibodies may be driving severe forms of COVID-19 [6-9]. These autoantibodies may also play a crucial role in the extended multi-organ illness persevering for months in patients with post Covid19 syndrome [6-9]. Furthermore, orthostatic cerebral hypoperfusion, hypotension, and small fibre neuropathy have been described [9]. The symptoms that occur in a large number of patients after severe COVID-19 disease, but also in many cases following mild Covid-19 infection, are similar to the clinical symptoms of other forms of infection-related chronic fatigue syndrome. Oxidative stress may contribute to this syndrome but in our experience replacement [15] of antioxidants and vitamins is not sufficient to achieve substantial improvement in clinical symptoms. In summary, the data presented in this study, and in other clinical studies with gold-activated serum suggest that raising pGSN levels in the body can contribute to the safe and effective preventive treatment of a number of diseases. We propose that this preliminary clinical study provides positive evidence for the use of gold–induced autologous conditioned serum in patients diagnosed with Post Covid-19 syndrome. Nevertheless, future double-blind placebo controlled comparative clinical trials must be performed to investigate the full potential of this new approach in comparison with the current standard therapies. A more detailed discussion of each patient group (amount of blood collected and amount of Goldic administered) and their pre-treatment therapies is needed. The whole discussion needs to be more precise and more critical.

Acknowledgement: We thank Harald Heidecke (Celltrend GmbH) for the analysis of the autoantibodies.

References

1. WHO Coronavirus Disease (COVID-19). Dashboard | WHO coronavirus disease (COVID-19) Dashboard.
2. Singhal T (2020) A review of coronavirus Disease 2019 (COVID-19). Indian J Pediatr 87: 281-286.
3. Martimbianco ALC, Pacheco RL, Latorraca COC et al (2021) Systematic reviews on interventions for COVID-19 have rarely graded the certainty of the evidence. Sao Paulo Med J. 139: 511-513.
4. Aiyegbusi OL, Hughes SE, Turner G, Ferreira RES, Riera R (2021) TLC Study Group. Symptoms, complications and management of long COVID: a review. J R Soc Med. 114: 428-442.
5. NICE. Common symptoms of ongoing symptomatic COVID-19 and post-COVID-19 syndrome COVID-19 rapid guideline: managing the long-term effects of COVID-19 guidance.

6. Liu Y, Sawalha AH, Lu Q (2021) COVID-19 and autoimmune diseases. Curr Opin Rheumatol. 33: 155-162.

7. Dotan A, Muller S, Kanduc D, David P, Halpert G, et al (2021) The SARS-CoV-2 as an instrumental trigger of autoimmunity. Autoimmun Rev. 20: 102792.

8. Pascolini S, Vannini A, Deleonardi G (2021) COVID-19 and Immunological Dysregulation: Can Autoantibodies be Useful? Clin Transl Sci. 14: 502-508.

9. Richter AG, Shields AM, Karim A, Birch D, Faustini SE, et al (2021) Establishing the prevalence of common tissue-specific autoantibodies following severe acute respiratory syndrome coronavirus 2 infection. Clin Exp Immunol. 205: 99-105.

10. Pascolini S, Vannini A, Deleonardi G, Ciordinik M, Sensolo A, et al (2021) COVID-19 and Immunological Dysregulation: Can Autoantibodies be Useful? Clin Transl Sci. 14: 502-508.

11. Schneider U, Wallich R, Felmet (2017) Gold-induced autologous cytokine treatment in Achilles tendinopathy. In: Canata G, d'Hooghe P, Hunt K (eds) Muscle and Tendon Injuries. Springer Berlin, Heidelberg: ISAKOS, 12: 411-420.

12. Schneider U, Kumar A, Murrell W, Ezekwesili A, Yurdi NA, et al (2021) Intra-articular gold induced cytokine (GOLDIC®) injection therapy in patients with osteoarthritis of knee joint: a clinical study. Int Orthop. 45: 497-507.

13. Feldt J, Donaubauer AJ, Welss J (2022) Anti-inflammatory effects of an autologous gold-based serum therapy in osteoarthritis patients. Sci Rep. 12: 3560.

14. Halpin SJ, McIvor C, Whyatt G, Adams A, harvey O, et al (2021) Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 93: 1013-1022.

15. Nittas V, Gao M, West EA, Ballouz T, Menges D, et al (2022) Through a Public Health Lens: An Umbrella Review. Public Health Rev. 43: 1604501.

16. Mandal S, Barnett J, Brill SE, Brown JS, Denneny EK, et al (2020) 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2020.

17. Benedek TG (2004) The history of gold therapy for tuberculosis. J Hist Med Allied Sci 59: 50-89.

18. Davis P (1988) Gold therapy in the treatment of rheumatoid arthritis. Can Fam Physician 34: 445-452.

19. Schneider U, Lotzof K, Murrell W, Ezekweslli A, Yurdi NA, et al (2021) Safety and efficacy of systemically administered autologous Gold-Induced Cytokines (GOLDIC®) CellR4 9: e3132.

20. Ordija CM, Chiou TT, Yang Z, Deloid GM, Valdo MDO, et al (2017) Free actin impairs macrophage bacterial defenses via scavenger receptor MARCO interaction with reversal by plasma gelsolin. Am J Physiol Lung Cell Mol Physiol 312: L1018-L1028.

21. Bär S, Daeffler L, Rommelaere J, Nuesch JPF (2008) Vesicular egress of non-enveloped lytic parvoviruses depends on gelsolin functioning. PLoS Pathog 4: e1000126.

22. Endres M, Fink K, Zhu J, Stagliano NE, Bondada V, et al. Neuroprotective effects of gelsolin during murine stroke. J Clin Invest 1999; 103: 347-354.

23. Zang N, Lin Z, Huang K, Pan Y, Wu Y, et al (2020) Biomarkers of unfavorable outcome in acute ischemic stroke patients with successful recanalization by endovascular thrombectomy. Cerebrovasc Dis 49: 583-592.

24. Vaid B, Chopra BS, Raut S, Sagar A, badmalia MD, et al (2020) Antioxidant and wound healing property of gelsolin in 3T3-L1 cells. Oxid Med Cell Longev 2020: 4045365.

25. Self WH, Wunderink RG, DiNubile MJ, Stossel TP, Levinson SL, et al (2019) Low admission plasma gelsolin concentrations identify community-acquired pneumonia patients at high risk for severe outcomes. Clin Infect Dis 69: 1218-1225.

26. Schneider U, Kumar A, Murrell W, Ezekwesli A, Yurdi NA, et al (2021) Intra-articular gold induced cytokine (GOLDIC®) injection therapy in patients with osteoarthritis of knee joint: a clinical study. Int Orthop.

27. Overmyer KA, Shishkova E, Miller IJ, Balnis J, Bernstein MN, et al (2021) A Large-Scale Multiomic Analysis of COVID-19 Severity. Cell Syst. 12: 23-40.e7.

28. Whetton AD, Preston GW, Abubeker S, Geifman N (2020) Proteomics and Informatics for Understanding Phases and Identifying Biomarkers in COVID-19 Disease. J Proteome Res. 19: 4219-4232.

29. Abers MS, Delmonte OM, Ricotta EE, Fintzi J, Fink DL, et al (2021) An immune-based biomarker signature is associated with mortality in COVID-19 patients. JCI Insight. 6: e144455.