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Safety and efficacy of systemically administered autologous Gold-Induced Cytokines (GOLDIC®)

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Abstract

Objective: **GOLDIC® is a novel technology involving the in vitro pre-conditioning of autologous patient whole blood with gold particles to induce autologous protein production. This study aimed to evaluate the safety and efficacy of GOLDIC® induced cytokines by intravenous injection into patients with various systemic diseases (allergies, fibromyalgia, psoriasis, rheumatoid arthritis, ulcerative colitis, polymyalgia rheumatica, osteoporosis and other diseases).**

Patients and Methods: **This is a prospective observational case series study of 55 patients suffering from various chronic systemic diseases who were treated with intravenous GOLDIC® injection. Inclusion criteria were having been diagnosed with a chronic systemic disease not efficiently controlled by the standard treatment. The mean age of participants was 55.9±18.4 years. Four consecutive intravenous GOLDIC® injections were carried out at 3 to 7 days intervals. The primary screening criterion was the treatment effectiveness documented by the Visual Analogue Scale (VAS) and global assessment. The initial findings were compared to the VAS values before the treatment and yearly over a period of at least 6 months and up to 6 years.**

Results: **Eight different disease groups were treated with the intravenous GOLDIC® method. There were statistically significant improvements in VAS scores following GOLDIC® treatment. There were no treatment-related adverse events and serious adverse events. The most impressive results were seen in patients with allergies and fibromyalgia.**

Conclusions: **GOLDIC® was confirmed as a novel method for conservative management of chronic systemic diseases. GOLDIC® produced a rapid and sustained improvement in symptomatology. This study is an open-label non-randomized, non-controlled study using a heterogeneous patient population. Future randomized-controlled trials may fully validate the safety and efficacy of GOLDIC® in different patient populations.**

Introduction

In the past twenty years the treatment using new biotechnologies which focus on amplifying the bodies natural healing properties to manage and modulate inflammation and to reduce pain has been a growing field of research[1]. Such applications, often using mesenchymal stem cells (MSCs), have been shown to be especially useful in orthopedics, sports medicine and regenerative medicine[1]. Many techniques and treatments have been assessed including stem cells or cell therapies, autologous blood-based products such as Platelet Rich Plasma (PRP) and Autologous Conditioned Serum (ACS). Stem cells and the novel therapeutic approach called "stem cell-based cell-free therapy", are often reliant on the autocrine production of growth factors, immu-

nomodulators and other bioactive molecules stored in extracellular vesicles (exosomes) which can be isolated and used instead of cells[2-4]. However, if the origin of exosomes is represented by embryonic or fetal cells, then there are many ethical and legal issues to overcome[5,6]. Autologous harvesting and priming of cells have many technical and methodological complexities and the long-term efficacy of the resulting exosomes is questionable if their use is not repeated at regular intervals[7]. When using MSCs, it has been proposed that the systemic paracrine modality is sufficient to produce therapeutic responses in some situations, while under other circumstances a cell-cell contact may be required[8]. Stem cells are often infused intravenously, but cells administered in this manner may experience rapid clearance or may be trapped in pulmonary capillary beds, which may explain their limited efficacy in some instances[9-11]. There has also been work on the use of regenerative medicine technology in the treatment of chronic pain, which includes the concept of neuroimmune regulation in pain relief[12].

The development of this novel GOLDIC® method to produce a conditioned serum rich in anti-inflammatory cytokines has proven to be very effective by enhancing the intrinsic regenerative capacity of the host plasma components. Gold compounds have been used for quite a long time in the treatment of different inflammatory disorders, especially in rheumatology[13,14]. The specialized gold particles, derived from the gold compound aurothiomalate, have been shown to inhibit the production of nitric oxide (NO) from chondrocytes. NO mediates the destructive effects of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-a), which include reduced collagen and proteoglycan production, apoptosis of chondrocytes and stimulation of matrix metalloproteinases[15]. *In vitro* studies have shown that incubation with gold particles inhibits catabolic factors, increases anti-catabolic and anabolic factors and also increases the level of gelsolin (GSN), which is a key protein in cellular metabolism[16]. The exact mode of action of the GOLDIC® procedure is not well understood, but *in vitro* studies have shown a significant increase in plasma GSN levels in the autologous serum as well as increased GSN levels in synovial fluid after each GOLDIC® injection. Both GSN and Granulocyte colony-stimulating factor (G-CSF) have been shown to promote tissue repair and regeneration[17-19].

The available data strongly support a crucial role for GSN in a variety of physiological and pathological processes including GSN involved as an actin-binding and depolymerizing protein, which exerts its effects in the form of intracellular cytoskeletal GSN and plasma GSN (pGSN)[20]. Of note, GSN is known to be a cytoplasmic regulator of actin organization, which regulates the viscoelasticity of the cell cytoskeleton and modulates important cell functions such as cell motility, phagocytosis and apoptosis. Most of the research, however, has focused on the extracellular actin-scavenger system (EASS) and on the role of pGSN in it, being responsible for rapid and continuous severing and removal of actin filaments released from dead cells into the bloodstream. The release of actin into the blood due to injury or illness-associated necrosis results in several pathophysiologic responses including increase of blood viscosity, activation of platelets and their aggregation, microvascular thrombosis, release of proinflammatory mediators such as thromboxanes, impairment of fibrinolysis, all of which result in a secondary tissue damage due to the high toxicity of actin[21]. Other studies have shown decreased pGSN concentrations in animals with sepsis, and treatment with GSN had a positive effect on the survival rate in these animals[22]. It has also been shown that pGSN serves as a buffer to intercept inflammatory reactions in rheumatoid arthritis; in addition, pGSN concentration has been shown to be decreased in various tissue degenerative diseases where GSN levels were reduced even more in the affected joints than in plasma[23].

In addition to its actin-sequestering properties, pGSN has also been reported to modulate the immune response by preferentially binding to bacterial cell walls, a process facilitated by the structural similarity between the intracellular GSN-binding molecules and bacterial endotoxins[24]. Moreover, pGSN has been shown to have a protective role in endotoxemia in mice[22]. These findings suggest the fundamental role of pGSN in the development and modulation of inflammatory responses and, consistent with these proposed functions, decreased blood GSN concentrations have been detected in serious clinical conditions such as acute respiratory distress syndrome, sepsis, major trauma, prolonged hyperoxia, malaria and liver injury[25]. Hospital inpatients with decreased pGSN levels have been observed to have higher mortality rates, longer hospital stay and longer ventilation time in Intensive

Care Units (ICUs) when compared to similar hospitalized patients with higher pGSN levels[15].

Evidence for the potential clinical utility of pGSN as a diagnostic tool has begun to accumulate in chronic diseases such as rheumatoid arthritis, where circulating pGSN concentrations are below normal values[13]. Given the fact that pGSN interacts with different cells of the immune system, pGSN may have regulatory and functional roles in chronic diseases such as Alzheimer's disease, rheumatoid arthritis, type 2 diabetes and cancer[26-28]. In a recent study conducted on patients with psoriatic arthritis, pGSN levels were decreased and showed a significant negative correlation with inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate, suggesting that pGSN may play an active role in chronic joint inflammation[29].

This correlation between pGSN and clinical conditions suggests the possibility for the therapeutic use of the GOLDIC® technique aimed at producing serum rich in anti-inflammatory cytokines and GSN in order to alleviate the destructive cascades in these acute settings or in chronic inflammatory conditions. The first GOLDIC® trial conducted in horses showed a significant improvement in lameness following treatment[30]. The first human clinical study investigated healing of Achilles tendinopathy and found significant clinical and Magnetic Resonance Imaging (MRI) improvements. As compared to other blood-based biological methods, GOLDIC® procedure has been shown result in the upregulation of pGSN and G-CSF, both of which are known to play an important role in tissue regeneration. In particular, all patients showed a complete regeneration of original tendon tissue one year after the treatment, and no severe adverse events were reported[14]. In a further clinical study conducted in patients with osteoarthritis of the knee, intra-articular GOLDIC® injections produced a rapid and sustained improvement in all symptoms, suggesting GOLDIC® as a promising option for the conservative management of moderate to severe osteoarthritis of the knee[31].

GOLDIC® is a CE marked and approved class IIb medical product. The GOLDIC® procedure is used mostly in musculoskeletal conditions such as osteoarthritis, tendinosis and muscle injury. The present study is a prospective observational case series study involving patients with various chronic systemic diseases. This study aimed to assess the safety and efficacy of intravenous GOLDIC® administration in improving the overall condition, altering the systemic pro-inflammatory state and harnessing the anti-inflammatory and immunomodulatory role of the immune system in tissue regeneration.

Patients and Methods

Patients

The objective of this study was to evaluate the safety and efficacy of intravenous GOLDIC® injection in patients with various systemic diseases. In order to evaluate the safety and efficacy of intravenous GOLDIC® injections, the investigators performed an observational study as a prospective case group study. All patients had been previously pre-treated unsuccessfully with various conventional treatments before taking part in this study. All patients were informed in detail about the benefits and risks of the treatment and gave their written informed consent to take part in the study. This study was carried out according to the guidelines of Good Clinical Practice (GCP)[32].

Preparation of GOLDIC®-Conditioned Serum

GOLDIC®-conditioned serum was prepared following a previously described procedure[14]. Briefly, 4x10 mL of peripheral blood was collected for each treatment directly into specifically designed GOLDIC® syringes. The syringes were then capped and incubated at 37°C for 24 hours. The syringes were then centrifuged, and the plasma was separated. The resultant GOLDIC®-treated plasma was then re-administered to the patients intravenously.

Administration of GOLDIC®-Conditioned Plasma

A total of 55 patients suffering from various systemic diseases (allergies, fibromyalgia, psoriasis, rheumatoid arthritis, ulcerative colitis, polymyalgia rheumatica, osteoporosis and other diseases listed in Table 1) were treated with GOLDIC® since 2014. The GOLDIC® was administered to the patients intravenously (into a peripheral arm vein) in the private practice of Prof. Dr. Ulrich Schneider. All patients had previously received conventional treatment for their specific disease without any improvement in symptoms. All patients received four consecutive intravenous GOLDIC® injections at 3 to 7 days intervals.

Table 1. Baseline characteristics of the study participants: age groups, gender, diseases and incidence of viral infections.

Baseline characteristics		N	%
Participants*		55	
Age Groups	0-25 years	4	7
	26-50 years	11	20
	51-65 years	22	40
	66 years and older	18	33
Gender	Male	28	51
	Female	27	49
Disease	Allergy	17	31
	Fibromyalgia	10	18
	Psoriasis	5	9
	Rheumatoid arthritis	5	9
	Ulcerative colitis	2	4
	Polymyalgia rheumatica	2	4
	Osteoporosis	2	4
	Other diseases**	12	22
Viral infections	Yes	28	51
	No	27	49

*The mean age of participants was 55.9 years (SD 18.4). **Other diseases included diabetes mellitus, scleroderma, Herpes zoster, Alzheimer's disease, Parkinson's disease, multiple sclerosis, chronic kidney disease, myositis, hemochromatosis, gout, glaucoma.

Screening, Safety and Ethical Criteria

The primary screening criterion was the demonstration of the effectiveness of GOLDIC® treatment by the documentation of the treatment outcome using the Visual Analogue Scale (VAS)[33] and the global assessment during the course of the study. The initial findings were compared to the values before the treatment and over a period of at least 6 months and up to 6 years for some patients. The safety of the procedure was assessed by the following tests: physical examination, vital function records and documentation of uncritical adverse events (AEs) and serious adverse events (SAEs). The safety monitoring was carried out for the entire investigation period. Local or systemic (outside the local treatment region) side effects were differentiated. The Medical Dictionary for Regulatory Activities (MedDRA) version 12.1 documentation system was used to define AEs and SAEs.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from all patients.

Statistical Analysis

The VAS values (ranging from 0 to 10) were statistically analyzed for all 55 patients participating in the study. This gave a VAS value for a minimum of 1 and a maximum of 7 timepoints. For all statistical tests α=0.05. Kolmogorov-Smirnov Goodness of Fit test gave no significance that the data were normally distributed. A non-parametric test was, therefore, used to calculate *p*-values. The data for each patient were paired over the different timepoints and calculated using the Wilcoxon signed-rank test. Patient numbers were low for 5 to 6 years and 6 to 7 years (n=5 and n=1, respectively). Statistical analyses were, therefore, not carried out at these timepoints. Statistical analyses were calculated out using Total Access Statistics 2000.

Results

In total, 8 different disease groups (7 specific disease groups plus the 'other' disease group) were treated with autologous intravenous GOLDIC® infusions. The mean age of participants was 55.9±18.4

years. The number of cases, age groups and sex distribution of the study participants are shown in Table 1. The evaluation of clinical effectiveness of GOLDIC® treatment using VAS scores is shown in Table 2, along with statistical analysis.

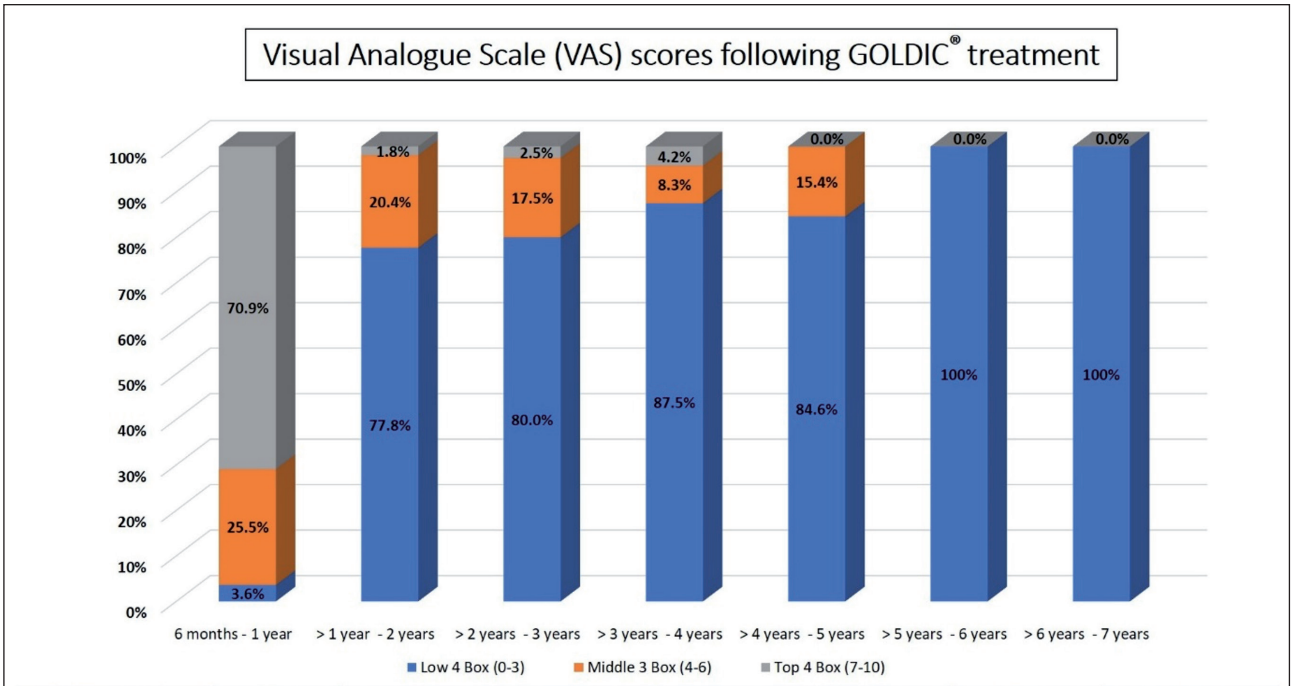
The VAS *p*-values were significant at all time-points (apart from 5 to 6 years and from 6 to 7 years, where statistics were not carried out due to low patient numbers) when compared to the VAS *p*-values at 6 months to 1 year. Figure 1 shows the overall VAS score found during the study, along with the statistical analysis.

Among 17 patients suffering from allergies who received GOLDIC® treatment, one reported no benefit (5.9%), no one reported mild benefit (0%), three reported average benefit (17.6%), six reported good benefit (35.3%) and seven reported excellent benefit (41.2%). The mean VAS score was 4.06 and the standard deviation (SD) was 1.09.

Among 10 patients suffering from fibromyalgia who received GOLDIC® treatment, no one reported no benefit (0%), one reported mild benefit (10%), no one reported average benefit (0%), five reported good benefit (50%) and four reported excellent benefit (40%). The mean VAS score was 4.20 and SD was 0.92.

In the entire cohort, 21 out of 55 patients (38%) reported transient hot flushes and fatigue after the first GOLDIC® injection. These symptoms resolved in all patients within a maximum of 24 hours. Moreover, 10 patients (18%) showed musculoskeletal stiffness and flu-like symptoms following the first GOLDIC® injection; 3 patients (5.45%) showed similar symptoms after the 3rd and 4th GOLDIC® injection, respectively. These symptoms resolved completely within 24 hours. Mild erythema at the injection site was seen in some patients, which resolved rapidly following GOLDIC® injections. None of the 55 patients in the study experienced any SAEs.

In the MedDRA documentation system, we found that the incidence of subsequent viral infections in all 55 patients was 0%. The cancer rate was also 0% in all 55 patients, which is below the average cancer rate in our population. During the follow-up period, two patients (3.6%) developed deep vein thrombosis, one patient (1.8%) was diagnosed with arrhythmia and one patient (1.8%) developed systemic lupus erythematosus (Table 3).



Median VAS	**7.0**	**2.0**	**2.0**	**2.0**	**2.0**	**2.0**	**n/a**
p-value compared to 6 months - 1 year period		**<0.0001**	**<0.0001**	**<0.0001**	**0.0015**	**n/a**	**n/a**

Figure 1. Visual Analogue Scale (VAS) scores following GOLDIC® treatment. Abbreviations: n/a, not applicable.

Table 2. Evaluation of the clinical effectiveness of GOLDIC® treatment based on Visual Analogue Scale (VAS) scores. Each box represents a category of VAS score.

Visual Analogue Scale (VAS)	Timepoints						
	6 months - 1 year	> 1 year – 2 years	> 2 years - 3 years	> 3 years - 4 years	> 4 years - 5 years	> 5 years - 6 years	> 6 years - 7 years
Number of patients assessed	55	54	40	24	13	5	1
Low 4 Box (0-3)	2 (3.6%)	42 (77.8%)	32 (80.0%)	21 (87.5%)	11 (84.6%)	5 (100%)	1 (100%)
Middle 3 Box (4-6)	14 (25.5%)	11 (20.4%)	7 (17.5%)	2 (8.3%)	2 (15.4%)	0 (0.0%)	0 (0.0%)
Top 4 Box (7-10)	39 (70.9%)	1 (1.9%)	1 (2.5%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Median VAS Score	7.00	2.00	2.00	2.00	2.00	2.00	n/a
SD	1.80	1.47	1.50	1.58	1.17	0.71	n/a
Probability, Wilcoxon to signed-rank test compared 6 months - 1 year		<0.0001	<0.0001	<0.0001	0.0015	n/a	n/a

Abbreviations: n/a, not applicable; SD, standard deviation.

Discussion

The therapeutic use of gold compounds 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 such compounds to the present day[34,35]. The introduction of autologous, closed processing GOLDIC® technology has enabled the benefits of gold compound therapy without the associated side effects. When using GOLDIC® technology, no gold compounds are readministered to the patient.

It is of particular interest that in previous studies the intra-articular GOLDIC® injection increased local GSN levels[31]. A possible increase in pGSN levels after intravenous GOLDIC® injection may partly explain the beneficial effects seen in participants of the present study. It is known that free or extracellular actin can decrease the activity of macrophages, thereby enabling infections to progress with greater speed and severity[36]. Importantly, pGSN can bind and cleave actin, thus reversing or minimizing such detrimental effects. It has also been shown that virus-induced actin processing increases when pGSN levels are low and that viral vesicular egress depends on pGSN functioning[37].

Perhaps, the most interesting observation in this study is the lack of viral infections seen following the GOLDIC® treatment. This may be explained by the antiviral effects of pGSN, which may be upregulated during the incubation of blood with GOLDIC®[38,39]. A normal level of pGSN has frequently been reported in the literature to show a range of beneficial effects, including reduction in brain inflammation and apoptotic signaling pathway activation in mice who had undergone brain ischemia[40]. The use of GOLDIC® may represent a valid intervention (upon confirmation coming from randomized control trials) in patients who have undergone a thermal shock, a traumatic injury to the central nervous system or a cerebrovascular accident. Low pGSN levels can represent a marker of poor prognosis in patients who have undergone an ischemic stroke and an endovascular thrombectomy[41]. It has also been shown that GSN protects against oxidative stress and enhances wound healing, which may be beneficial in overall general health[42]. It has also been suggested that low pGSN levels may result in more severe clinical outcomes in patients suffering from pneumonia, which could have potential implications in the treatment of COVID-19[43]. The observations about the importance of pGSN in various diseases suggest a wide range of potential applications in the future of GOLDIC® in routine clinical practice.

In this study, the intravenous administration of autologous gold-induced cytokines using

Table 3. Disease occurrence in patients who received GOLDIC® treatment.

After treatment	N	%
Viral infections		
Yes	0	0
No	55	100
Cancer		
Yes	0	0
No	55	100
Other diseases		
Deep vein thrombosis	2	3.6
Arrhythmia	1	1.8
Systemic Lupus Erythematosus	1	1.8

GOLDIC® procedure has shown impressive overall clinical efficacy, accompanied by a very low incidence of minor side effects. The side effects observed were all transient peripheral irritations to the skin consisting of mild erythema at the intravenous injection site. This may have been a physiological reaction of the body to the GOLDIC®-activated serum, but it could equally be a simple injection site reaction seen in many intravenous infusions.

However, this pilot study is limited by its open-label, non-randomized and non-controlled design. Moreover, we enrolled a heterogeneous patient population. Future randomized-controlled trials (RCTs) may fully validate the safety and efficacy of GOLDIC® in different patient populations.

Conclusions

In summary, the data presented in this study suggest that the use of GOLDIC® to treat a range of chronic diseases is safe and effective and has a clear beneficial effect. The most impressive results were seen in patients suffering from allergies and fibromyalgia. Other systemic diseases were also treated with good success (Table 1). The mid-term trend shows an ongoing effectiveness of GOLDIC® treatment for up to 6 years. This is the first description of the clinical safety and efficacy of GOLDIC® procedure, making this paper an important contribution to the future wider clinical use of gold-activated autologous plasma using the GOLDIC® method and to a better understanding of the roles of pGSN in health and diseases.

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Author contributions:
Ulrich Schneider: Conception and design of the study, data acquisition and analysis, drafting of the article, final approval for publication. Kevin Lotzof and William Murrell: data acquisition. Emily Goetz von Wachter: data acquisition and analysis. Peter Hollands: data analysis, drafting of article, revision of the article, final approval for publication.

Ethical Statement:
The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee(s) and with the Helsinki Declaration (as revised in 2013).

Informed consent:
Written informed consent was obtained from all patients.

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Conflict of Interest:
Ulrich Schneider is the inventor of GOLDIC® and CEO of iRegMed. Emily Goetz von Wachter is employed by iRegMed. Kevin Lotzof, William Murrell and Peter Hollands declare that they have no conflicts of interest to disclose.

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