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Commentary

Systems Medicine and the Contribution of Low Dose Pharmacology in Paediatrics

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Abstract

The introduction of the diagnostic-therapeutic approach based on Systems Medicine into the medical scenario has allowed us to deeper investigate into the concept of the human organism as a set of interconnected networks. This wide vision, in addition to shedding new light on the interpretation of pathological manifestations, allows us to set up new therapeutic strategies based on the management of alterations in the networks identified as involved in the onset and progression of the disease. The tool that, to date, can allow to set up network regulation treatments is Low Dose Medicine, a therapeutic approach based on low-dose pharmacology. The use of low doses signaling molecules is the physiologically most appropriate option for the management of network alterations. In the pediatric field, numerous experiences have confirmed the validity of this approach. A preclinical study and a Delphi Consensus have provided clear evidence on the action mechanism and clinical application of a low-dose medication (Citomix®) for the prevention and early treatment of Recurrent Respiratory Infections. The consensus was based on preclinical data and was aimed to collect clinical experiences with Citomix® about the biological capacity to modulate the immune response in the presence of infectious agents. The cornerstone of the consensus was the validation of the use of Citomix® as an option for the prevention and early add-on treatment of RRIs; the positive result which emerge from the vote of the statements constituting the consensus confirmed the validity of the investigated option.

Keywords

Low Dose Medicine, Low Dose Pharmacology, Recurrent Respiratory Infections, Citomix, Immunomodulation, Delphi Consensus

1. Introduction

The Systems (or network) Medicine is a relatively recent branch of medical research [1] which draws inspiration from developments in basic research, in particular Systems Biol- and all the "omics" disciplines [2], such as genomics, metabolomics, transcriptomics, which allow for the acquisition of large amounts of information at the molecular level on the individual person and the individual pathology.

Given these premises, it is possible to define Systems Medicine as an interdisciplinary field of study in which human body systems (networks) are studied and considered as a part of an "integrated whole", incorporating biochemical, physiological and environmental interactions [3].

In recent years, System Medicine has shown a notable development, both in terms of research and practical applica-

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tions; among these, Low Dose Medicine (LDM) deserves particular attention.

LDM represent a successful example of integration between Molecular Biology and Psycho-Neuro-Endocrine-Immunology (PNEI) [4-8] grounded on the results of re- in the field of low dose pharmacology.

Within the LDM paradigm [9], a key role is played by PNEI and its main unifying element: the crosstalk between the psycho-neuro-endocrine systems and the immune system, managed by signaling molecules such as neuropeptides, hormones, cytokines, growth factors that play a decisive role in determining the state of health or disease [10-16].

An altered crosstalk, caused by an imbalance in the concentration of specific signaling molecules, is crucial, for example, in the pathogenesis of inflammatory, allergic and autoimmune diseases.

Preserving or restoring the physiological concentration of messenger molecules is the key step for the maintenance or recovery of the physiological homeostatic balance which describes the healthy condition [17-19].

In homeostatic conditions, the concentrations of signaling molecules are included in a specific physiological range (nanograms-picograms), above or below which a disease condition can occur. Given these theoretical premises, a substantial line of research has developed regarding the possibility of a therapeutic use of low doses biological molecules that, orally administered, can control and guide cellular functions to restore the original physiological conditions.

The mechanism of action of low dose signaling molecules consists in the modulation of the receptor's response involved in the pathways that physiologically involve the signaling molecules themselves.

By virtue of their low concentration, the receptor activation which occurs in such a way does not trigger saturation mechanisms and consequent freezing of the receptor itself but, on the contrary, amplifies its physiological response. Furthermore, the use of physiological doses substantially reduces the risk of adverse events.

2. LDM and Scientific Research

Sixteen years of scientific research in the field of LDM [20-37] have demonstrated the validity of the conceptual approach, and the efficacy and safety of pharmacological treatments based on the oral administration of low doses signaling molecules. Current scientific research highlights the high Immunostimulating and immunomodulating capacity of low-dose interleukins and interferons, hormones and neurotrophins. Evidence shows that orally (sublingually) administered signaling molecules can effectively modulate immune response. Due to its high accessibility, the oral mucosa is an elective gate for the administration of small active peptide molecules. The mechanism of action for orally administered peptides involves the uptake of the molecule by oral antigen-presenting cells (APCs) which present the signaling molecule itself to immunocompetent T cells within oropharyngeal lymph nodes, inducing a specific immune response.

Many experimental studies conducted so far have focused on pathologies characterized by an immune imbalance that is reflected mainly (although not exclusively) in an imbalance between the cytokines expressed by the two main lymphocyte subpopulations: Th1 and Th2. The LDM therapeutic rationale consists in the promotion of immune homeostasis by administering specific low dose cytokines.

For example, in a murine model of allergic asthma (20), the imbalance with increased production of IL-4 and IL-5 was found to be pivotal for the onset of the biological events that characterize the allergic pathology such as increased differentiation, maturation and migration of eosinophils at the medullary level.

The administration of IL-12 and IFN-gamma at low doses induces a significant reduction in the synthesis of IL-4 and IL-5 and a clear decrease in the number of eosinophils in the bronchoalveolar lavage fluid.

Some preclinical studies have shown that, using physiological sub-nanomolar doses of low dose hormones (FSH - follicle-stimulating hormone, Beta-estradiol, and Progesterone), it is possible to counteract certain imbalances of the PNEI axes involved in pathologies such as Polycystic Ovary Syndrome (PCOS) [31], Stress-related Hypothalamic Amenorrhea [32] and Endometriosis [33].

The use of pharmacological aids such as low-dose hormones with bioregulatory capacity appear to be therapeutic tools of great interest alone (in conditions of preserved capacity for self-regulation) or in overlapping with hormone replacement therapy (in conditions of advanced state of endocrine dysregulation) to reduce – if possible – the dosage of the replacement hormone and, consequently, the possible onset of dose-related side effects.

Biological activity is also described for low dose neurotrophins: in vitro and in vivo studies [36] demonstrated the efficacy of low dose BDNF (Brain-Derived Neurotrophic Factor) in supporting neuroprotection mechanisms and in particular a positive effect has been highlighted control of ROS expression, vitality of cortical neurons and astrocytes, and proliferation of astrocytes.

3. LDM Clinical Applications in the Pediatric Field

All the studies conducted so far show the ability of signaling molecules to modulate the cellular response in a highly selective way.

Basic and clinical research conducted to date in the field of LDM shows encouraging signs in terms of efficacy, compliance and safety which are of particular interest in the pediatric field.

An example of pediatric clinical application of LDM is in

Atopic Dermatitis management [35]. Treatment with low dose cytokines (IL-12 and IFN-γ) was evaluated in a pediatric population affected by chronic atopic dermatitis. The results show that low dose cytokines treatment reduced the severity of the disease and contributed to maintaining a Low Disease Activity (LDA) in the treatment-free at the follow-up period. These results were transduced in a progressive improvement in the quality of life of subjects treated with low dose throughout the investigation period.

The LDM approach has also proven effective in the management of stress-induced hypothalamic amenorrhea [32], a condition in which the absence of the menstrual cycle is determined by an imbalance in the neuroendocrine response to stress with overexpression of opioid peptides and blockade of the pulsatility of hypothalamic GnRH (Gonadotropin Releasing Hormone) and pituitary LH (Luteinizing Hormone) hormones release. The use of weak estrogens in low doses such as epimestrol and estriol has proven capable of rebalancing the GnRH-LH axis by increasing the release of the latter. The use of low-dose estradiol has proven equally effective by increasing the sensitivity of the GnRH receptors at the hypothalamic and pituitary levels, supporting the synthesis of LH and FSH. Clinical data demonstrate that low-dose estradiol can restore the normal connectivity of the HPG axis compromised by stress and, because of that, responsible for the onset of stress-induced hypothalamic amenorrhea.

4. Highlight: LDM for Recurring Respiratory Infections (RRIs) Management

Respiratory infections are a demanding challenge for physicians. Commonly, a relative immune defect sustains their recurrence. At present, there is no standardized treatment for their prevention acting on the immune system [36].

Recurrent Respiratory infections (RRIs) are a very common clinical condition in childhood, with an important social and economic impact. It is estimated that about 25% of children under 1 year old and 6% of children during the first 6 years of life have RRIs, making them one of the most common reasons for pediatric medical visits in the early years of life [38].

RI treatment is generally based on symptomatic drugs (e.g. acetaminophen) and antibiotics administration, but frequently without precise indication. Therefore, prevention of RRI is at present a goal in clinical practice. Bacterial lysates are also used with mild results in reducing respiratory morbidity in clinical practice. Thus, there is a high interest in preventive and alternative treatment by doctors. In this regard, immunomodulants are widely used in common practice [36].

The administration of cytokines modulates the immune response in a complex manner, as demonstrated in a study by Tagliacarne et al [36] conducted at the Laboratory of Clinical Immunology of the Pediatric Clinic of the University of Pavia on adenoid tissue taken from children with recurrent inflammation of the airways in whom adenoidectomy had been indicated. Adding known concentrations of LDM multicomponent drug Citomix® (Guna S.p.a. Milan, Italy) to the cell culture of the adenoid tissue demonstrated an immune modulatory action characterized by:

a) increase in Interleukin 6 and Interferon-gamma with a reduction in the initial phases of Interleukin 10 useful for enhancing the anti-viral response.
b) increased production of IgA and IgM;
c) proliferation of B lymphocyte subpopulations.

These results are in line with the data of the first clinical experiences on children with recurrent upper respiratory tract infections who, following cycles of therapy and prophylaxis according to the following protocol, significantly decreased the days of fever and absence from school and were treated much less frequently with antibiotics, therefore in line with the most current recommendations for less use of these drugs, especially in the early ages of life, motivated above all by the increase in bacterial resistance phenomena worldwide.

Based on this background and on the real-life experience with Citomix® in the management of RRI [39, 40], a Delphi Consensus on the management of RRIs using Citomix® was designed involving a large group of Italian primary care, private practice, and hospital/university pediatricians [41].

A modified Delphi process was used to reach consensus within a panel of Italian specialists (112 Pediatricians) on the preventive and overlapping approach with Citomix® as a new intervention model for the management of IRRs. The voting panel was composed of general practitioners (64%), free choice (27%) and hospital/university pediatricians (9%).

A scientific committee analyzed the literature, determined the areas requiring investigation (in accordance with the results of the multiple-choice questionnaire) and identified two macro-topics of interest:

a) IRRs as disease (definition and diagnosis)
b) treatment and prophylaxis of IRRs.

Statements for each of these topics were then formulated and validated. The Delphi method involves rounds of questions submitted to the panel experts using an online platform. In the first round of voting, consensus was reached for all the statements.

In accordance with their usual methods of managing IRRs and with current clinical evidence, the panel members provided their feedback on their agreement with each statement of the questionnaire.

The experts evaluated and voted on 18 statements and reached a consensus on all 18; the first 6 statements were related to the pathology itself (Topic A) and the following 12 (Topic B) related to the current methods of treating IRRs and the options offered by Citomix®. For each statement, consensus was considered to have been reached with the achievement of agreement by at least 66.6% of the expert group and the acceptance of the scientific committee.

To calculate the consensus, the sum of the votes expressed with the values of 4 and 5 on the Likert scale corresponding

to: “in agreement” and “in strong agreement” was considered (Table 1).

Table 1. *Statements summary and voting results for each statement [41].*

	1) Strongly disagree	2) Disagree	3) Undecided	4) Agree	5) Strongly Agree	Sum of votes 4-5	Consensus reached if ≥ 66,6%
Topic A: IRR disease							
Statement 1: Recurrent Respiratory Infections (RRIs) are a clinical condition of frequent observation in children and are the main causes of morbidity in high-income countries. Therefore, RRIs represent an important challenge for pediatricians. In addition, RRIs have a significant social and economic impact consequent to high access to medical care, school absenteeism and absence from work for parents.	1/112	0/112	1/112	45/112	65/112	110	98,2%
Statement 2: Among individual risk factors, immunological inexperience plays a key role along with early community entry, passive smoking and environmental pollution, low birth weight or prematurity and/or the presence of atopy.	1/112	0/112	1/112	38/112	72/112	110	98,2%
Statement 3: The first diagnostic step for RRIs is basically based on excluding chronic pathological conditions, such as recurrent infections exclusively in a site (e.g., recurrent rhinosinusitis, recurrent otitis media, recurrent pharyngo-tonsillitis), known primary or secondary immunodeficiencies (including IgA deficiency), cystic fibrosis and/or CFTR-protein disorders, primary ciliary dyskinesia, non-cystic fibrosis-related bronchiectasis, genetic pathologies, known malformations of the cardio-respiratory system, neuromuscular pathologies, and other pre-existing chronic lung diseases.	1/112	3/112	5/112	56/112	47/112	103	92,0%
Statement 4: The criteria for defining a child with RRIs in pediatric age are: 1) 1-3 years: 6 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year 2) 3-6 years: 5 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year 3) 6-12 years: 3 or more respiratory tract infections (1 of which may be pneumonia, including severe pneumonia) in a year or 2 mild cases of pneumonia confirmed by clinical criteria and/or x-ray in a year	1/112	2/112	4/112	59/112	46/112	105	93,7%
Statement 5: Most respiratory infections in children are caused by viruses (e.g., rhinovirus, res-	1/112	1/112	3/112	46/112	61/112	107	95,5%

	1) Strongly disagree	2) Disagree	3) Undecided	4) Agree	5) Strongly Agree	Sum of votes 4-5	Consensus reached if ≥ 66,6%
Topic A: IRR disease							
piratory syncytial virus, adenovirus, influenza virus)							
Statement 6: RRIs may be associated with worsened respiratory function, abuse and misuse of antibiotics, and deterioration of the quality of life not only of the child but of the entire family	1/112	1/112	1/112	58/112	51/112	109	97,3%
Topic B: IRR treatment and prophylaxis							
Statement 7: RRIs treatment is generally based on symptomatic drugs (e.g., ibuprofen, paracetamol, and inhaled or systemic corticosteroids) and antibiotics, often inappropriately	2/112	12/112	5/112	60/112	33/112	93	83,0%
Statement 8: Effective RRIs prevention strategy should be a primary objective in clinical practice. For this purpose, conventional immunomodulants for RRIs prophylaxis are commonly used in daily practice.	1/112	7/112	9/112	66/112	29/112	95	84,8%
Statement 9: A recent Inter-Society Consensus recognized as weakly effective the RRIs prophylaxis based on the use of: 1) Biological Response Modifiers (BRMs) 2) Probiotics, prebiotics, symbiotics, postbiotics 3) Lysates and bacterial extracts 4) Vitamins and trace elements 5) Vaccination against flu and pneumococcus 6) Nasal lavages with hyaluronic acid, thermal waters, resveratrol 7) Reduction of risk factors 8) Adeno/tonsillectomy 9) • Antibiotic prophylaxis	2/112	15/112	17/112	52/112	26/112	78	69,6%
Statement 10: Complementary or alternative immunomodulation interventions for RRIs prophylaxis might be instead an option.	0/112	2/112	2/112	62/112	47/112	109	97,3%
Statement 11: Oral administration of cytokines has been shown to be effective in modulating the immune response.	0/112	1/112	3/112	56/112	52/112	108	96,4%
Statement 12: Citomix is a low-dose multicomponent product based on cytokines and components of natural origin that can modulate the immune response by acting on both innate and adaptive immunity.	0/112	0/112	2/112	59/112	51/112	110	98,2%
Statement 13: Citomix has a good safety and tolerability profile	0/112	0/112	1/112	54/112	57/112	111	99,1%
Statement 14: Citomix could improve the early response to pathogens	0/112	0/112	1/112	61/112	50/112	111	99,1%
Statement 15: Citomix could be considered in RRIs management	0/112	0/112	2/112	55/112	55/112	110	98,2%

Topic A: IRR disease	1) Strongly disagree	2) Disagree	3) Undecided	4) Agree	5) Strongly Agree	Sum of votes 4-5	Consensus reached if ≥ 66,6%
Statement 16: In RRIs prophylaxis, the recommended dosage of Citomix is 5 granules per day for 12 weeks.	0/112	0/112	7/112	59/112	46/112	105	93,7%
Statement 17: Citomix could be added in the early treatment of acute RRIs.	0/112	0/112	10/112	57/112	45/112	102	91,1%
Statement 18: In the early treatment of the acute episode of RRIs, the recommended dosage of Citomix is 10 granules per day 2 times per day for 2-3 days, continuing with 5 granules 2 times per day for 5-7 days.	0/112	2/112	8/112	63/112	39/112	102	91,1%

a) The statements relating to the IRR pathology showed high levels of agreement, with a consensus ranging from 92% to 98.2%.
b) The statements regarding the treatment and prophylaxis of IRR also showed very high levels of agreement, with a consensus ranging from 69.6% to 99.1%.

Through the Delphi Method it was possible to reach consensus among doctors on the most significant aspects of the current management of IRR management and the possibility of a new approach towards pediatric patients subject to IRR both in terms of prevention and overlapping with current therapies based on the use of Citomix®.

The consensus was unanimous, among Pediatricians, in identifying the prevention and overlapping approach based on Citomix® for the management of RRIs. This Consensus collected the level of agreement expressed by a large panel of pediatricians who have developed a solid experience in the use of Citomix® to manage children with RRIs. The high level of agreement reached in a single voting round allows to endorse the use of Citomix® in clinical practice for the prevention and early treatment in overlapping of RRIs. It is important to underline that the opinions of the panel members, expressed in the form of voting, derive both from their experience, acquired from daily practice, and from the evidence derived from preclinical and clinical studies. In conclusion, Citomix® represents, for a significant sample of pediatricians, a valid tool for both prevention and overlapping treatment of RRIs.

5. Conclusions

Starting from a series of basic evidence proven with scientifically correct methodologies, LDM has increasingly carved out a specific role in the field of clinical medicine. Its applications and boundaries are still largely to be studied and controlled but current evidence already allows us to consider it, in some specific pathologies, as an important complementary therapy that, in connection with the "classic" one, can be useful to improve the quality of life of patients, reduce the risk of unwanted side events and adverse reactions, reduce the use of drugs that are certainly useful but potentially harmful, maintain the patient in LDA (Low Disease Activity) after reaching the remission of symptomatology (such as, for instance in Rheumatoid Arthritis patients who had undergone remission after biological drugs or conventional therapy) [34], and contribute to reduce the costs of therapies, especially chronic ones. Regarding the specific topic of RRIs, the Delphi consensus results have verified the initial hypothesis: it is therefore possible to include Citomix® among the drugs that can be used for prevention or combined with other interventions (overlapping) to enhance their efficacy (add-on treatment) in the early treatment of RRIs.

Abbreviations

APCs	Antigen-Presenting Cells
BDNF	Brain-Derived Neurotrophic Factor
FSH	Follicle-Stimulating Hormone
GnRH	Gonadotropin Releasing Hormone
LDA	Low Disease Activity
LDM	Low Dose Medicine
LH	Luteinizing Hormone
PCOS	Polycystic Ovary Syndrome
RRIs	Recurrent Respiratory Infections

Author Contributions

Sergio Bernasconi is the sole author. The author read and approved the final manuscript.

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Conflicts of Interest

Prof. Sergio Bernasconi carries out consultancy activities for Guna S.p.a.

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Biography

Sergio Bernasconi is retired full Professor of Pediatrics He has been President of the Italian Society for Pediatric Endocrinology and Diabetology (ISPED), Member of the Council and of the DTC Committee of the European Society for Pediatric Endocrinology (ESPE), Editor in chief of the Italian Journal of Pediatrics (currently Editor Emeritus), Chairman of The Department of Pediatrics of the Universities of Modena and Parma (Italy). He is honorary member of the University of Chieti (Italy) and he received the "Outstanding Clinician Award" from ESPE. He is author and/or co-author of about 500 scientific papers published on international journals and he is member of Editorial Boards of national and international journals. He has been Chair and Invited Speaker in national and international Conferences and Congresses.

Research Field

Sergio Bernasconi: Pediatric Endocrinology, Auxology, Clinical Genetics, Complementary Medicine