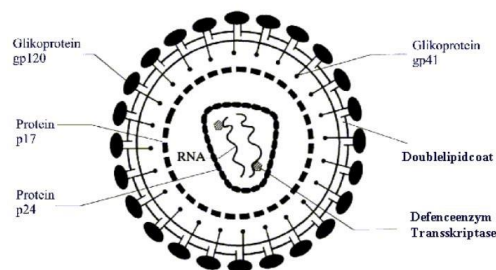




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Preclinical Investigation Report TMA-Z¹ - MEGAMIN ACTIV on Viral Diseases



¹ TMA-Z: Tribomechanical Activated Zeolite (Clinoptilolite)

1. Introduction

This report focuses on the mineral product TMA-Z – MEGAMIN ACTIV which resulted from the investigation in vitro and in vivo Humans.

TMA-Z is a natural mineral product, tribomechanical activated vulcano mineral zeolite. The specifically used zeolite is called Clinoptilolite.

The cellactive natural product TMA-Z is a new antioxidant with far higher capacities than any other known antioxidants. The tribomechanical activated and polarised natural minerals zeolite act as a stabilizer on the cellmembrane and a ionic exchanger with active surface.

Beyond investigation has shown a lot more performance mechanisms of this substance TMA-Z, which have partly been published already in famous medical journals.

1.1. Basic Substance

Zeolites are natural aluminosilicates with tetrahedra linked structures containing AlO_4 and SiO_4 . Even Natural Clinoptilolite shows precious capacities for instance as an antidiarrhoe substance. Clinoptilolite decreased the amount of diseases and death caused by intestinal diseases in swine, rats and calves distinctively. Beyond, various investigations showed the important role of zeolite in regulating the immune system.

Zeolites are natural microporous silicaminerals, from colourless to white or light red with possible partly changes of colour, caused by enclosures and/or other minerals. In chemical compound these are A1-Na or A1-Ca silicates, which foam when exposed to heat and seem to dissolve.

Ueki and co-workers (38.) reported that silicea, silicates and aluminosilicates act as non specific immunostimulators similar to superantigens [10,11]. Superantigens (SAG) are a class of immunostimulatory and disease-causing proteins of bacterial and viral origin with the ability to activate relatively large fractions (5-20%) of the T cell population. Activation requires simultaneous interaction of the SAG with V β domain of T cell receptor. Multiple viral diseases, as for instance AIDS, lead to elevation of oxidative stress.

1.2. TMA-Z – MEGAMIN ACTIV

TMA-Z indicates the tribomechanical activated mineral zeolite, concrete Clinoptilolite.

The tribomechanical activation of substances, especially of mineral origin, is the indication of the type of processing which is used to activate the particle surface and the structure of the Zeolites when producing the polarised substance TMA-Z.

While processed, the particles of the substance are exposed to multiple collisions and frictions in a very short period of time (0,0001 – 0,001 sec.). This causes a significant change of their geometry. Through these relative movements of one particle amongst the surface of another particle, the structure of the crystal chain on the surface is destroyed or effectively ripped

open, which leads to a change of the physical, physico-chemical and energetic capacities of the material. The energetic capacities are driven by some 100%.

As an accompanying circumstance of this process, the material is also grinded and micronised, a mentionable amount of particles in submicron range as well as nanophases (particles less than 400nm) arise.

1.3. About the HIV- Disease

Viral disease e.g. infectious mononucleosis, herpes, hepatitis, AIDS and others, lead to an elevated oxidative stress. Persons with AIDS are often very underfed and are abandoned as such ones at raised measure oxidative stress. With these sick, the level of antioxidative defense is lowered and level that lipid hydroperoxide raised (J.L. McLemore, 1998). It is proved that the ROS cause an activation of the transcription factor NF-Kappa B, after what the replication of the virus is activated. The result is the apoptosis, especially the CD4 T-lymphocytes. For this reason, antioxidants have an optimal effect in the case of virus illnesses, e.g. AIDS, more infectious mononucleosis, herpes, and so forth (E. Peterhans, 1997).

A new generation of antioxidants to a silicon base become ascribed a number of positive effects to the oxyreductive protection system. Siliciumhold antioxidants perform a protection system to the B cells of the Langerhans islands (G. Papaccio, 1998) and show a favorable influence to the regulation of the bloodsugar spectrum.

2. The product

Through tribomechanical activation of the clinoptilolite its capacities are elevated many times.

Finished preclinical testing of the basic substance tribomechanical activated zeolite (clinoptilolite) TMA-Z, aluminosilicates, including toxicological and pharmacokinetic studies, have not shown any toxic effect of this substance. It has to be emphasized that no lethal dose could be found.

At present TMA-Z products are registered with the Austrian Ministry of Health as a food supplement, should be used as an adjuvans and/or roborans to support medical standard therapies. This also to obtain an improvement of the well being and at the same time supporting healing and rehabilitation of very difficult chronic diseases.

3. Previous Results

TMA-Z proves to be a possibly extraordinarily impressive product. It shows the following qualities among others:

1. Antioxidant effect
2. Immunostimulated
3. Antiviral effect
4. Antibacterial effect
5. Antitumor effect

1. Oxydoreductive effect

Hepatitis B, C, and Aids are caused through oxidative stress. With these diseases a processing is a good addition therapy with antioxidants. We can stimulate our antioxidative protection system through the effort of TMA-Z. TMA-Z stimulates three enzymes. Superoxide dismutase (SOD) and Glutathione Peroxidase (GPx) are two enzymes, which are responsible for the adsorption of free radicals. Glutathione Reduktase can eliminate damages.

2. Immunologic effect

We can stimulate our immune system, concerning T-Lymphocytes CD4+ und CD 8 as Th 1 and Th 2 cells.

Immunologic consequences and hypotheses

Pavelic and coworkers (39.) recently realized that tribomechanically activated natural zeolite clinoptilolite actually showed unexpected positive effects in treatment of cancer, infectious and autoimmune diseases. How then can similar agents be so toxic in one case or helpful in another? This is not unprecedented in biomedical sciences at all. Radiation is very toxic and carcinogenic, yet is also used to cure cancer. Chemotherapy agents are also very toxic and carcinogenic but also can be used to cure cancer. Often, weakened versions of very toxic agents can be used to cure disease. Vaccines are other example of the same principle.

What can be the mechanism of action of orally applied zeolites. This required collaborative projects between physicians, chemists and physicists. First, physicochemical analysis of TMA-Z was performed. The results of such analysis showed that activated zeolite had same crystalline structure, chemical composition, particle charge, surface chemistry and catalytic activity as inactive "as received" sample. The only difference between two samples was in mean particle size. Activated zeolite showed large proportion of particles smaller than 5 microns with at least 20% of submicron particles by weight and some nanoparticles. Particles also had very irregular rough shape. Biochemical analysis showed that particles do not enter human body in significant concentrations, but can be incorporated into lipid liposomes and model membrane systems.

This strongly suggested possibility of indirect action through the modification of immune system response. It is well known that particles smaller than 5 microns and submicron particles penetrate into gut associated lymphoid tissue (GALT). There, immune system cells encounter numerous antigens. It is necessary for gut immune system not to react with food. Therefore, any antigen which enters GALT results in tolerance. For instance feeding diabetic mice with insulin helps alleviate the progression of disease. Feeding arthritic mice with collagen II helps alleviate arthritis. This happens due to suppression of the immune system response at the location of the fed antigen (pancreas for insulin feeding, joints for collagen feeding). Oral tolerance mechanisms are nicely described in H. Weimer, Immunology Today, Vol. 18, July 1997, p. 335-343.

Even if orally fed TMA-Z does cause oral tolerance several questions remained to be helpful in so many diseases. Physicians observed positive effects in TMA-Z treatment of diabetes, Crohn's Disease, psoriasis and other autoimmune diseases. Even more controversial, positive effects were observed in cancer treatment where enhancement of the immune response should be mechanism.

How can same agent enhance immune response in one case and repress it in other? Literature analysis by authors of this report identified that indeed antigens do exist that cause such diverse response of the immune system. Such unusual antigens are termed superantigens. Superantigens (SAG) are a class of immunostimulatory and disease causing proteins of bacterial or viral origin with the ability to stimulate and activate large fractions (5-20%) of the T cell population. Activation requires simultaneous interaction of the SAG with the V β domain of the T cell Receptor (TCR) and with the major histocompatibility complex (MHC) class II molecules on the surface of an antigen presenting cell (APC). Recent advances in the structure of such complexes showed that superantigens surpass normal activation of T cells by physically binding TCR and APC. This first results in strong immune response with the subsequent anergy and death of T cells.

Actually numerous clinical trials are currently performed to test the efficiency of genetically engineered weaker forms of SAG in treatment of autoimmune diseases, infectious diseases and cancer. In autoimmune diseases, such treatment kills many Th1 CD4+ T cells. Less active Th2 and Th3 cells then predominate. Such cells secrete immunosuppressive cytokines TGF β and IL-10 and further suppress immune system self-destructive activity. Good manuscript describing mechanism of action of SAG is: H. Li. Et al., *Ann. Rev. Immunol.* Vol. 17 ; pp. 435-466 (1999). While this could explain TMA-Z activity in autoimmune disease, it should be counterproductive to kill Th 1 cells in cancer treatment. But not quite so. Killing of Th 1 cells in cancer patients results in strong activation of natural killer cells (NK cells) and natural killer activated T+1 cells. Such cells are actually much more efficient in the killing of cancer. Of course, this also mean that one cannot kill tumors which are resistant to NK cells with TMA-Z. Also it suggest that more immunogenic tumors such as melanoma, adenocarcinoma or glioblastoma are more susceptible to TMA-Z treatment,, as was observed by Dr. Ivkovic.

But, are there any experimental data showing that aluminosilicates are superantigens? It was shown in the article in *Immunology*, Vol. 82(2); pp. 332-335 (1994) and *Int. J. of Oncology*, Vol. 12(6); pp. 1355-1359 (1998) that silicates indeed behaved as the superantigen. Do we have any data which would suggest that TMA-Z act on immune system. Yes we do. Another type of immune cells, B cells also can be activated or deactivated by SAG. Type of cells that react with superantigen are so called CD5 B cells. Pavelic and coworkers showed that such cells are activated in hepactomyzed rats. Many patients also observed mild fever during the first days of using TMA-Z that later disappeared. Future experiments will directly test immune mechanism of action of TMA-Z.

In order to fight immune response in autoimmune diseases, TMA-Z therefore should be able to cause apoptosis of cells. This was also shown by our research. Many different cells in cell cultures were killed after they were placed in contact with TMA-Z. TMA-Z also induced a growth arrest. The mechanism of action was also tested. TMA-Z inhibited antiapoptotic protein kinase B/akt. In some cases tumor suppressor molecules p21 and p27 were also induced. This probably can also inactivate JNK-1 kinase which is needed to activate highly destructive Th1 CD4 cells. Further research in this area is also needed. Animal model studies with diabetes prone mice, cancer inoculated mice and other diseases models are under way. To conclude, we believe that orally applied TMA-Z penetrates into GALT where it contacts and modifies immune system. This results in oral tolerance. Since TMA-Z might be a superantigen it reduces immune system response to many different antigens and therefore is helpful in treatment of many autoimmune diseases. Such inactivation of some immune cells might also activate others, which can enhance TMA-Z activity against some cancers. Same

mechanism might be helpful in activation of the immune response against such pathogens such as hepatitis.

In addition, accumulating evidence has indicated that zeolites play an important role in regulation of the immune system. Ueki and co-workers reported that silicea, silicates and aluminosilicates act as non specific immunostimulators similar to superantigens [10,11]. Superantigens (SAG) are a class of immunostimulatory and disease-causing proteins of bacterial and viral origin with the ability to activate relatively large fractions (5-20%) of the T cell population. Activation requires simultaneous interaction of the SAG with V β domain of T cell receptor and with major histocompatibility complex (MHC) class II molecules on the surface of antigen presenting cells [10]. Macrophages, that belong to the class II MHC antigen presenting cells, a temporary activation with strong inflammable reflex becomes followed of the T cells.

Direct interaction of silicate particles with cells other than lymphocytes was also identified and described. It seems that mineral particles can trigger alterations in gene expression by initiating signalling events upstream of gene transactivation [16]. It was indeed shown that exposure of cells to silicate particles leads to activation of mitogen activated protein kinase (MAPK), protein kinase C and stress activated protein kinases [17]. Important transcription factors such as AP-1 or NF κ B are also activated and expression of pro-inflammatory cytokines such as IL-1 α , IL-6 or TNF α was enhanced [18]. Modifications of receptor activation kinetics or activity of integrins can be responsible for the observed behaviour. Alternatively, particles engulfed by phagocytosis were shown to stimulate production of reactive oxygen species [19]. It was recently shown that redox regulation of gene expression is a general phenomenon in most cells.

The above mentioned knowledge about zeolites and other silicates prompted us to test the biological activity of natural clinoptilolite. Mechanical treatment of natural clinoptilolite was used to produce small-sized particles (MZ), that were tested for eventual toxicity and anti cancer activities in vivo. Here we provide evidence that orally applied natural clinoptilolite was non toxic and useful in cancer treatment in animal models. Additional in vitro tissue culture experiments with different cancer cell lines indicated that TMA-Z treatment modifies intracellular signalling pathways leading to inhibition of survival signals and induction of tumor suppressor genes.

3. Antiviral effect

The antiviral effect of TMA-Z was observed in laboratory experiments at Herpes, Papilloma and some other viruses, the mechanisms could not be arrested clearly. The adsorption of herpes viruses through TMA-Z was observed.

Antiviral effect was further observed with patients. The patients showed very fast liberation of illness symptoms and doctors reported the patients overall status to be visibly improved within a few weeks, also in most cases the virus load was decreased.

4. Adjuvants and antibacterial agents

Silicate as a superantigen induces *in vitro* polyclonal human T cell activation. Therefore, silica and related substance such as silicate possess “adjuvant effects” (Aikohh et al 1998). Immunization of rabbits and mice with zeolite adsorbed *Trypanosoma gambiense* inactive vaccine showed remarkable protective ability with high level of agglutination titer remained in immune system (Ryu, Shaey, 1981; Ryu, Shaey, 1980).

Clinoptilolite inhibits *Salmonella typhimurium* survival and growth in agricultural soil. The response was highly positively correlated with the change in moisture content and the size of zeolite (Ricke et al 1995).

Antibacterial properties of zeolites were used in balloon catheter for controlling urinary tract infection. This catheter showed a bactericidal effect against *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Escherichia coli* *in vitro*. It might be useful for patients who need long term balloon catheter indwelling (Uchida et al 1992).

Ag-zeolite (Zeonic) – a new antimicrobial material combined with a commercial tissue conditioner showed strong antifungal effect. It inhibits *Candida albicans* growth, acid production and it is a potential aid in denture plaque control (Nikawa et al 1997).

Double blind cross-over clinical study showed that silver-zeolite in mouthrinse significantly reduces plaque formation (Morishita et al 1998).

5. Antitumor effect

Excerpt from that studies from Dr. Miroslav Colic (40), - “Effect of TMA-Z on tumor cell in laboratory experiments.”

The aim of our study was to evaluate the effect of TMA-Z on proliferation rate of several human tumor cells *in vitro*.

Materials and methods

Reagents. Fetal bovine serum (FBS) and RPMI was purchased from Sigma, DMEM from Gibco-BRL, 0.45 μ m filters from Millipore.

Cells and cell culturing. *In vitro* experiments were carried out on three human tumor cell lines: HeLa (cervical carcinoma), HT-29 and CaCO-2 (colon carcinoma). HeLa was cultured in RPMI while HT-29 and CaCO-2 cells were cultured in DMEM. Both media were supplemented with 10% fetal bovine serum (FBS), 100U/ml penicillin and 100 μ g/ml streptomycin. The cells were incubated in humidified chamber at 37°C with 5% CO₂.

Proliferation assay. To examine the effect of the TMA-Z on cell growth we plated 2×10^5 cells/well in fouruplicate onto 96 microwell plates. Following overnight incubation we

replaced the medium with the medium previously treated with different TMA-Z→ concentrations. The medium was pre-treated with 0.5, 5.0 and 50.0 mg/ml TMA-Z→ for a period of 18 hours with continuous shaking. After incubation the substance was pelleted by centrifugation (5000g), while the medium (supernatant) was sterilized by filtering through 0.45 µm Millipore filters. To evaluate the cell growth rate the MTT (thiazol blue) test was performed after 72-hour incubation in TMA-Z→ treated medium. MTT assay detects dehydrogenase activity in viable cells. For this purpose the TMA-Z→ pre-treated medium was discarded and MTT was added to each well at the concentration of 20 µg/40 µl. After four hours of incubation the precipitates were dissolved in 160 µl of dimethyl-sulphoxide. The absorbency was measured on ELISA reader at 570 nm. Cell proliferation was expressed as a ratio between the cell viability of TMA-Z→ pre-treated cells and control cells (non-treated cells) expressed in percentages.

Results

The effect of TMA-Z→ was tested on three human cell lines: HeLa, CaCO-2 and HT-29. When TMA-Z→ was added directly onto growing cells no effect on cell proliferation was observed in concentration range from 10^{-6} to 10^{-2} . However, the growth inhibition was dramatically reduced in a dose dependent manner with doses ranging from 10^{-2} to 10^2 (data not shown). Cell death was probably due to insolubility of the compound which physically damaged the cells when added to cultures in high concentrations. For this reason, in further experiments the cells were incubated with TMA-Z→ pre-treated medium 24 hours after they were seeded on microtiter plates.

The summarized results are shown in Figure 1. The growth inhibition is apparent on all three cell lines and in all three concentrations being most significant on HeLa cells.

Conclusion

The growth of HeLa, CaCO-2 and HT-29 human tumor cells was inhibited by incubation with TMA-Z→ pre-treated medium in a dose-dependent manner

Effect of TMA-Z→ on human cell lines

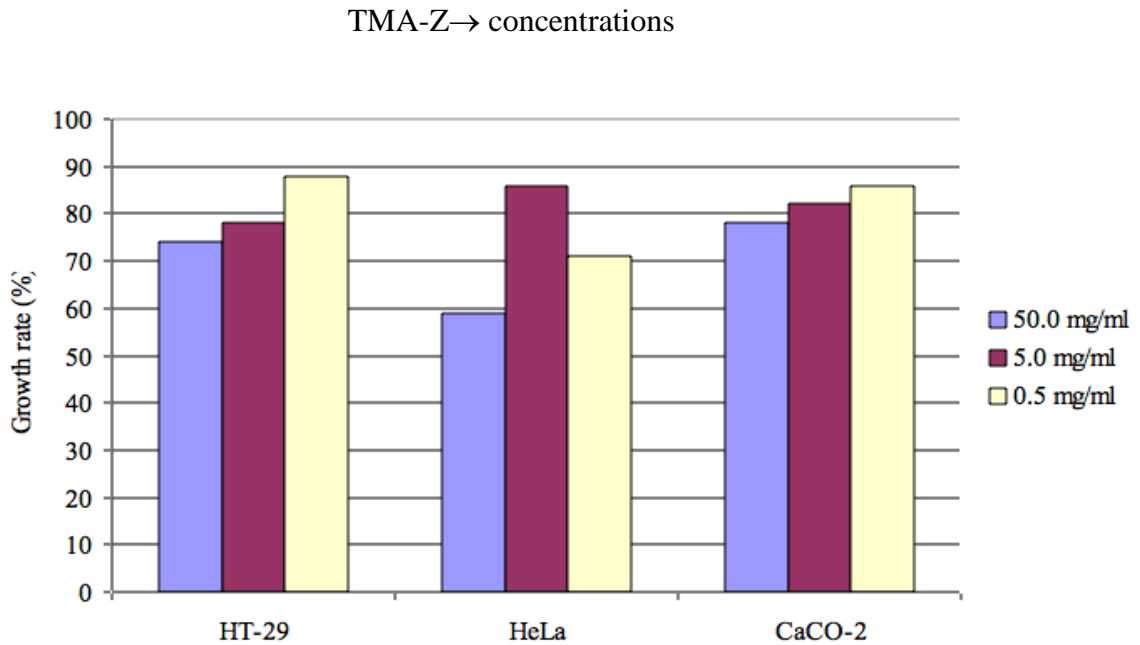


Figure 1. Effect of TMA-Z→ on proliferation of human tumor cell lines

4. Suggestion for clinical studies on HIV

Multiple tests in small groups of patients with Hepatitis C and Aids have shown encouraging results.

For clinical tests we recommend the following dosage:

Daily Intake	Regularity Every hour (08:00 until 22:00)	Entire daily dosage.	Duration of first part of treatment
32 Capsulas 10 Teaspoons solubed in one liter	2 Capsulas To be taken 4 to 6 times a day stirred in a glas of water or juice (non acid, non milk)	12,8 Gramms TMA-Z VM1 capsulas 20 Gramms TMA-Z VM1 Powder	Two months

Before intake and after every 14 days of treatment the following values should be checked:

1. Titar-Virus in blood
2. T CD 4 in blood
3. T CD 8 in blood
4. Specific antibody for HIV-neutralisation
5. Th 1 and Th 2
6. TAS (Total Antioxydant Status – not obligatory)

These values should be checked one month after intake started.

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