Human Cytomegalovirus: The Cause Of IgA Nephropathy

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Abstract

Objective: The present publication investigates the relationship between the presence of Human cytomegalovirus (HCMV) in renal tissue and IgA Nephropathy (IgAN).
Methods: A systematic review and re-analysis of studies which investigated the relationship between HCMV and IgAN was conducted aimed to answer the following question. Is there a cause-effect relationship between HCMV and IgAN? The method of the conditio sine qua non relationship was used to proof the hypothesis whether the presence of HCMV guarantees the presence of IgAN. In other words, without HCMV no IgAN. The mathematical formula of the causal relationship k was used to proof the hypotheses is, whether there is a cause-effect relationship between HCMV and IgAN. Significance was indicated by a p-value of less than 0.05.
Results: The studies analysed were able to provide strict evidence that HCMV is a necessary condition (a conditio sine qua non), a sufficient condition and a necessary and sufficient condition of IgAN. Furthermore, the cause-effect relationship between HCMV and IgAN (N=37, k =+0.514619883, p value (k) =0.001746216) was highly significant.
Conclusions: On the basis of published data and ongoing research, sufficient evidence is given to conclude that HCMV is the cause of IgA Nephropathy.

Keywords: Cytomegalovirus, IgA Nephropathy, Causal relationship

1. Introduction

IgA Nephropathy (IgAN) or Berger's disease characterized by the presence of IgA-dominant or co-dominant immune deposits within glomeruli (Roberts, 2014) was first described by the renal pathologist Jean Berger (1930–2011) in the year 1968 (Berger et al., 1968; Feehally et. al., 2011). Berger's disease is a chronically progressive disease and a very common (McGrogan et al., 2011) primary glomerulonephritis.The incidence of IgA nephropathy as the leading causes of end-stage renal disease is at least 2.5/100000/year in adults (McGrogan et al., 2011). At present, treatment options for Berger's disease are still very limited. Disease management mainly consists of reducing proteinuria by angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), controlling blood pressure, lipid levels and other supportive treatment. Persistent proteinuria (=1 g/d and eGFR > 50 ml/min per 1.73m 2) in IgA Nephropathy patients (Palevsky et al., 2013) is treated with a 6-month course of corticosteroids therapy. Regarding treatment options for immunoglobulin A nephropathy there are encouraging results and increasing evidence of the efficacy and safety of CMV drugs like ganciclovir (Ortmanns et al., 1998) and leflunomide (Lou et al., 2006; Rong et al., 2007; Wu et al., 2016; Min et al., 2017). Human cytomegalovirus (HCMV) infects more or less asymptomatically (Priel et al., 2015) about 50% to 90% of the adult (Yi et al., 2013; Najafi et al., 2016) human population. To date, even if an increasing amount of literature suggests that HCMV is involved in the aetiology of IgAN the pathomechanism of IgAN is still an unresolved issue. Gregory et al. documented in 1988 (Gregory et al., 1988) the first description of mesangial staining of polyclonal antihuman cytomegalovirus (anti-HCMV) antibodies in IgAN patients. However, with regard to the presence of HCMV in the renal tissue of IgAN, conflicting results (Okamura, 1989; Dueymes et al., 1989; Tomino et al, 1989; Béné et al., 1990; Lai et al., 1990) have been documented in the literature while using a variety of different techniques. Hung et al. in 1996 (Hung et al, 1996) were not able to provide evidence of a higher frequency of positive antibody titres for several common viruses in IgAN patients. Especially, the lack of a uniform operational definition of positivity in IgA Nephropathy and the use of different methodological

approaches and other factor may have been a source of bias. Finally, an impressive HCMV PCR DNA presence in a high percentage of IgA Nephropathy cases was reported by Müller et al. in 1991 and in 1992.

2. Material and methods

2.1. Material

2.1.0. Search strategy

To answer the questions addressed in this paper, the electronic database PubMed was searched for appropriate studies conducted in any country which investigated the relationship between human cytomegalovirus and glioblastoma multiforme i. e. sero-epidemiologically or by polymerase chain reaction (PCR) et cetera. The search in Pubmed was performed while using some medical key words like "case control study" and "cytomegalovirus" and "IgA Nephropathy" et cetera. The articles found where saved as a *.txt file while using the support of Pubmed (Menu: Send to, Choose Radio Button: File, Choose Format: Abstract (text). Click buttom "create file"). The created *.txt file was converted into a *.pdf file. The abstracts where studied within the *.pdf file. Those articles were considered for a re-view which provided access to data without any data access barrier. Additionally the reference list of identified articles was used as a potential source of articles appropriate for this study.

2.1.1. The 2x2 table

The meaning of the abbreviations a_t, b_t, c_t, d_t, N_t of the data table used are explained by a 2 by 2-table **Table 1**.

Table 1. The sample space of a contingency table.

		Conditioned B_t (Outcome)		
		Yes = +1	**Not = +0**	**Total**
Condition A_t (risk factor)	**Yes =+1**	a_t	b_t	$\mathbf{A_t}$
	Not = +0	c_t	d_t	$\underline{A}_t$
	Total	$\mathbf{B_t}$	$\underline{B}_t$	$\mathbf{N_t}$

In general it is $(a_t+b_t) = A_t$, $(c_t+d_t) = \underline{A}_t$, $(a_t+c_t) = B_t$, $(b_t+d_t) = \underline{B}_t$ and $a_t+b_t+c_t+d_t=N_t$. Equally, it is $B_t+\underline{B}_t = A_t + \underline{A}_t = N_t$. In this context, it is $p(a_t)=p(A_t \cap B_t)$, $p(A_t) = p(a_t)+p(b_t)$ or $p(A_t)= p(A_t \cap B_t)+ p(b_t) =p(A_t \cap B_t)+p(A_t \cap \underline{B}_t)$ while $p(A_t)$ is not defined as $p(a_t)$. In the same context, it is $p(B_t) = p(a_t)+p(c_t) = p(A_t \cap B_t) +p(c_t)$ and equally that $p(\underline{B}_t) = 1- p(B_t) =p(b_t)+p(d_t)$. Furthermore, the joint probability of A_t and B_t is denoted by $p(A_t \cap B_t)$. Thus far, it is $p(A_t \cap B_t) = p(A_t) - p(b_t) = p(B_t) - p(c_t)$ or in other words it follows that $p(B_t) + p(b_t) - p(c_t) = p(A_t)$. Thus far, define $\Lambda = p(b_t) - p(c_t)$, Einstein's term Λ under conditions of probability theory and we obtain $p(B_t) + \Lambda = p(A_t)$. In general, it is $p(a_t)+p(c_t)+p(b_t)+p(d_t) = 1$.

2.1.2. Association, correlation and causation

Random variable may stand in a relationship to one another in such a way that the one random variable has influence on another random variable which does not arise simply by chance. In general, association can be treated as the absence of independence. The absence of independence alone must not proof causality for sure. Correlation which is not identical with causation measures only a specific form of association. In this context, "Pearson correlation" is the most often quoted correlation and assumes a linear trend between random variables. A cause effect relationship between random variables highly probable is a statistically significant causal relationship k is given and if at the same time evidence is provided that there is a significant conditio sine qua non relationship, or a significant conditio per quam relationship, or both, or a significant exclusion relationship et cetera between investigated random variables. Otherwise, conclusion drawn may be fallacious.

2.1.3. The study of Müller et al. 1991 (Germany)

The data as provided by Müller at al. 1991 are viewed by the **Table 2**.

Table 2: The Study of Müller et al. (DE 1991)

		IgA Nephropathy <B>		
		Yes	No	Total
HCMV PCR DNA Positive <A>	Yes	10	**3**	13
	No	**0**	6	6
	Total	10	9	19

k = **0.71611487**

p value (k) = **0.00179949**

WITHOUT <A> NO <B>.

p (SINE) = 1

X^2(SINE) = **0.025**

IF <A> THEN <B>

p (IMP)= 0.84210526

X^2 (IMP)= **0.48076923**

<A> is SINE and IMP of <B>

p(SINE ^ IMP) = 0.84210526

X^2(SINE ^ IMP) = **0.50576923**

2.1.4. The study of Müller et al. 1992 (Germany)

The data as provided by Müller at al. 1992 are viewed by the **Table 3**.

Table 3: The Study of Müller et al. (DE 1992)

		IgA Nephropathy <B>		
		Yes	No	Total
HCMV PCR DNA Positive <A>	Yes	14	**4**	18
	No	**5**	14	19
	Total	19	18	37

k = **0.51461988**
p value (k) = **0.00174622**

WITHOUT <A> NO <B>.
p (SINE) = 0.86486486
X^2(SINE) = **1.06578947**

IF <A> THEN <B>
p (IMP)= 0.89189189
X^2 (IMP)= **0.68055556**

<A> is SINE and IMP of <B>
p(SINE ^ IMP) = 0.75675676
X^2(SINE ^ IMP) =**1.74634503**

2.2. Methods

2.2.1. Statistical analysis

All statistical analyses (Barukčć, 1989; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c) were performed with Microsoft Excel version 14.0.7166.5000 (32-Bit) Software (Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05. The probabilities of the contingency table are viewed by the following table (**Table 4**).

Table 4. The probabitlities of a contingency table

		Conditioned B_t		
		Yes = +1	**No = +0**	**Total**
Condition A_t	**Yes =+1**	$p(a_t) = p(A_t \cap B_t)$	$p(b_t)$	$p(A_t)$
	No = +0	**$p(c_t)$**	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	**1**

2.2.2. Independence

In the case of independence of A_t and B_t (Kolmogorov, 1933) it is generally valid that

$$p(A_t \cap B_t) \equiv p(A_t) \times p(B_t) \tag{1}$$

2.2.3. Exclusion (A_t excludes B_t and vice versa relationship)

The mathematical formula of the *exclusion* relationship (A_t excludes B_t and vice versa) of a population was defined as

$$p(A_t \mid B_t) \equiv \frac{b_t + c_t + d_t}{N_t} \equiv 1 - p(a_t) \equiv p(b_t) + p(c_t) + p(d_t) \equiv p(c_t) + (1 - p(B_t)) \equiv p(b_t) + (1 - p(A_t)) \equiv +1 \tag{2}$$

and used to proof the hypothesis: A_t *excludes* B_t and vice versa.

2.2.4. Necessary condition (conditio sine qua non)

The mathematical formula of the *necessary* condition relationship (conditio sine quam non) of a population was defined as

$$p(A_t \leftarrow B_t) \equiv \frac{a_t + b_t + d_t}{N_t} \equiv p(a_t) + p(b_t) + p(d_t) \equiv p(a_t) + (1 - p(B_t)) \equiv +1 \tag{3}$$

and used to proof the hypothesis: *without* A_t *no* B_t .

2.2.5. Sufficient condition (conditio per quam)

The mathematical formula of the *sufficient* condition relationship (conditio per quam) of a population was defined as

$$p(A_t \rightarrow B_t) \equiv \frac{a_t + c_t + d_t}{N_t} \equiv p(a_t) + p(c_t) + p(d_t) \equiv p(d_t) + p(B_t) \equiv +1 \tag{4}$$

and used to proof the hypothesis: *if* A_t *then* B_t .

2.2.6. The X^2 goodness of fit test of a necessary condition

The justification of inferences or procedures which extrapolate from sample data to the population or general facts is a central problem of statistics itself. The problem of induction is not addressed, nor is the article concerned with details to justify the correctness of statistical methods. Despite disagreements, it is insightful to recall that the relation between data and hypotheses is of use to determine how believable a hypothesis is and a way to avoid invalid inference. But, as can be imagined, insufficient statistical methods (i.e. risk ratio) used to analyze data but confounding too has influence on a valid inference especially in studies concerned with causality and it is hard to avoid incorrect conclusions in principle. A good study design has the potential for reducing confounding but does not guarantee valid inference. Still, hypotheses can be evaluated in the light of empirical facts while using some specific statistical methods. The chi square is such a statistical method which can be used for discrete distributions like the binomial distribution and the Poisson distribution but requires a sufficient sample size (n >30) in order to be valid. The *chi-square Goodness of fit test* compares how well an *empirical distribution* fits a theoretical distribution. The Null hypothesis of Chi-Square goodness of fit test (Yamane, 1973) assumes that there is no significant difference between an empirical distribution and a theoretical distribution. In contrast to this, the chi-square test for independence compares two sets of data. For continuous distributions, the Kolmogorov-Smirnov (Sachs, 1992) and Anderson-Darling goodness of fit tests (Sachs, 1992) are used. Under conditions where the chi-square goodness of fit test (Pearson, 1900) cannot be used it is possible to use an approximate and conservative (one sided) confidence interval known as *the rule of three* (Rumke, 1975; Hanley et al. 1983; Louis, 1981; Jovanovic et al., 1997). According to the definition of the conditio sine qua non relationship it is

$$p\left(A_t \cap B_t\right)+\left(1-p\left(B_t\right)\right)\equiv+1 \tag{5}$$

or

$$p\left(A_t \cap B_t\right)+1-p\left(B_t\right)\equiv+1 \tag{6}$$

Either something is a necessary condition of something else *or* it is not, a third is not given. Rearranging this equation, we obtain the essential foundation of the conditio sine qua non relationship as

$$p\left(A_t \cap B_t\right)=p\left(B_t\right) \tag{7}$$

and equally our starting point of the derivation of chi-square value of the conditio sine qua non relationship. Multiplying equation before by the population or sample/population size N, it is

$$N\times p\left(A_t \cap B_t\right)\equiv N\times p\left(B_t\right) \tag{8}$$

or

$$N\times p\left(A_t \cap B_t\right)-N\times p\left(B_t\right)=0 \tag{9}$$

The square operation yields

$$\left(N\times p\left(A_t \cap B_t\right)-N\times p\left(B_t\right)\right)\times\left(N\times p\left(A_t \cap B_t\right)-N\times p\left(B_t\right)\right)=0\times 0 \tag{10}$$

Dividing by $N\times p(B_t)$ we obtain

$$\frac{\left(N\times p\left(A_t \cap B_t\right)-N\times p\left(B_t\right)\right)^2}{N\times p\left(B_t\right)}=0 \tag{11}$$

which is equivalent with

$$\frac{\left(a_t-\left(B_t\right)\right)^2}{\left(B_t\right)}=\frac{\left(a_t-\left(a_t+c_t\right)\right)^2}{\left(B_t\right)}=\frac{\left(c_t\right)^2}{\left(B_t\right)}=0 \tag{12}$$

Adding $((b_t+d_t)-(\underline{B}_t))^2/\underline{B}_t = ((b_t+d_t)-(b_t+d_t))^2/\underline{B}_t = 0$ yields

$$\frac{\left(c_t\right)^2}{\left(B_t\right)}+0=0+0 \tag{13}$$

Using *the continuity correction*, the chi-square value of a conditio sine qua non distribution before changes to

$$\chi^2\left(SINE\right)\equiv\frac{\left(c_t-\left(\frac{1}{2}\right)\right)^2}{\left(B_t\right)}+0=0 \tag{14}$$

The use of the continuity correction should follow the rules of statistics as established and valid today. This definition of the X^2 distribution of a *conditio sine qua non* distribution (degrees of freedom = 2-1=1) is more precise than already published formulas. In this context, it is not necessary to improve the definition of the X^2 distribution of a *conditio per quam* distribution as already published. A statistically significant conditio sine qua non relationship demands a causal relationship k which is $k > 0$, otherwise the result of a study should be treated with cautious.

2.2.7. The X^2 goodness of fit test of the exclusion relationship

According to the definition of the exclusion relationship it is

$$p\left(b_t\right)+p\left(c_t\right)+p\left(d_t\right)\equiv+1 \tag{15}$$

Rearranging this equation, we obtain

$$p(b_t) = 1 - p(c_t) - p(d_t) = 1 - \left(p(c_t) + p(d_t)\right) \equiv 1 - p(\underline{A}_t) = p(A_t) \tag{16}$$

and

$$p(c_t) = 1 - p(b_t) - p(d_t) \equiv 1 - \left(p(b_t) + p(d_t)\right) = 1 - p(\underline{B}_t) = p(B_t) \tag{17}$$

The chi square goodness of fit test of the exclusion relationship can be derived as follows.

$$\begin{aligned} N \times p(b_t) &= N \times p(A_t) \\ \left(N \times p(b_t) - N \times p(A_t)\right) &= 0 \\ \left(N \times p(b_t) - N \times p(A_t)\right) \times \left(N \times p(b_t) - N \times p(A_t)\right) &= 0 \times 0 \\ \frac{\left(N \times p(b_t) - N \times p(A_t)\right)^2}{N \times p(A_t)} &= \frac{0}{N \times p(A_t)} = 0 \end{aligned} \tag{18}$$

$$\chi^2(b_t) = \frac{\left(N \times p(b_t) - N \times p(A_t)\right)^2}{N \times p(A_t)} = \frac{\left(b_t - (a_t + b_t)\right)^2}{A_t} = \frac{\left(-(a_t)\right)^2}{A_t} = 0$$

$$\chi^2(b_t) = \frac{\left(-(a_t) - 0{,}5\right)^2}{A_t} = 0$$

and as

$$\begin{aligned} N \times p(c_t) &= N \times p(B_t) \\ \left(N \times p(c_t) - N \times p(B_t)\right) &= 0 \\ \left(N \times p(c_t) - N \times p(B_t)\right) \times \left(N \times p(c_t) - N \times p(B_t)\right) &= 0 \times 0 \\ \frac{\left(N \times p(c_t) - N \times p(B_t)\right)^2}{N \times p(B_t)} &= \frac{0}{N \times p(B_t)} = 0 \end{aligned}$$

$$\chi^2(b_t) = \frac{\left(N \times p(c_t) - N \times p(B_t)\right)^2}{N \times p(B_t)} = \frac{\left(c_t - (a_t + c_t)\right)^2}{B_t} = \frac{\left(-(a_t)\right)^2}{B_t} = 0 \tag{19}$$

$$\chi^2(c_t) = \frac{\left(-(a_t) - 0{,}5\right)^2}{B_t} = 0$$

The chi square value with degree of freedom 2-1=1of the exclusion relationship with a *continuity correction* can be calculated as

$$\chi^2(\mathrm{EXCL}) = \frac{\left(-(a_t) - 0{,}5\right)^2}{A_t} + \frac{\left(-(a_t) - 0{,}5\right)^2}{B_t} \tag{20}$$

A statistically significant exclusion relationship demands a causal relationship k which is **k < 0** otherwise the results of a study should be interpreted with some cautious.

2.3.5. The mathematical formula of the causal relationship k

The mathematical formula of the causal relationship k (Barukčć, 1989; Barukčć, 2017a; Barukčć, 2017b; Barukčć, 2017c; Barukčć, 2018a; Barukčć, 2018b; Barukčć, 2018c) is defined *at every single event*, *at every single Bernoulli trial t*, as

$$k\left(A_t, B_t\right) \equiv \frac{\left(p\left(A_t \cap B_t\right) - \left(p\left(A_t\right) \times p\left(B_t\right)\right)\right)}{\sqrt[2]{\left(p\left(A_t\right) \times p\left(\underline{A}_t\right)\right) \times \left(p\left(B_t\right) \times p\left(\underline{B}_t\right)\right)}} \tag{21}$$

where A_t denotes the cause and B_t denotes the effect. The chi-square distribution can be applied to determine the significance of causal relationship k. Correlation (Pearson, 1896) is not causation, causation is not correlation. The relationship between correlation and causation is discussed already in many publications. This does not necessarily imply that repeating itself over and over again may contribute anything new to further scientific progress.

2.3.6. The chi square distribution

The following critical values of the chi square distribution as visualized by **Table 5** are used in this publication.

Table 5. The critical values of the chi square distribution (degrees of freedom: 1).

	p-Value	One sided X^2	Two sided X^2
The chi square distribution	0,1000000000	1,642374415	2,705543454
	0,0500000000	**2,705543454**	**3,841458821**
	0,0400000000	3,06490172	4,217884588
	0,0300000000	3,537384596	4,709292247
	0,0200000000	4,217884588	5,411894431
	0,0100000000	5,411894431	6,634896601
	0,0010000000	9,549535706	10,82756617
	0,0001000000	13,83108362	15,13670523
	0,0000100000	18,18929348	19,51142096
	0,0000010000	22,59504266	23,92812698
	0,0000001000	27,03311129	28,37398736
	0,0000000100	31,49455797	32,84125335
	0,0000000010	35,97368894	37,32489311
	0,0000000001	40,46665791	41,82145620

3. Results

3.1. A human cytomegalovirus infection *is the cause* of IgA Nephropathy.

Claims.
Null hypothesis:
A cytomegalovirus infection is not the cause of IgA nephropathy, k = 0.
Alternative hypothesis:
A cytomegalovirus infection is the cause of IgA nephropathy, k ≠ 0.
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.
The results of the re-analyses of the relationship between HCMV and IgAN are viewed **Table 2** and by **Table 3**. The sample size study of Müller et al. in 1991 is less than n = 30 **(Table 2)** and was analyzed according to *the rule of three*. The result is significant at 0.05 level. According to Müller et al., 1991: *without* HCMV *no* IgAN. The same study provided significant result according to the rule of three of a sufficient condition. In other words, *if* HCMV is present in kidney tissues, *then* IgAN (k = +0.71611487, p value (k) = 0.00179949). The study of Müller et al., 1992 **(Table 3)** provided significant result of necessary condition relationship (p(HCMV ← IgAN) = 0.86486486, X^2(HCMV ← IgAN) = 1.06578947, k = +0.51461988, p value (k) = 0.00174622), of a sufficient condition relationship (p(HCMV → IgAN) = 0.89189189, X^2(HCMV → IgAN) = 0.68055556, k = +0.51461988, p value (k) = 0.00174622), and of a necessary and sufficient condition relationship (p(HCMV ←→ IgAN) = 0.75675676, X^2(HCMV → IgAN) = 1.74634503, k = +0.51461988, p value (k) = 0.00174622). In other words, according to Müller et al., 1992 **(Table 3)** *without* HCMV *no* IgAN and equally *if* HCMV is present in kidney tissues, *then* IgAN is present too. In other words, HCMV *is the cause of* IgAN.
Q. e. d.

3.2. Etanercept is highly effective against HCVM.

Claims.
Null hypothesis:
Coronary heart diseae (CAD) and an etanaercept therapy are excluding each other.
Alternative hypothesis:
Coronary heart diseae (CAD) and an etanaercept therapy are not excluding each other. .
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.
Proof.
HCMV is the cause of atherosclerosis (Barukčć, 2018d) and thus far of coronary heart disease and at the end of coronary events. An appropriate immunosuppressive therapy should be able to decrease the incidence of CAD events. Tumor necrosis factor (TNF-a) mediates host-resistance against microorganisms, is elevated during acute viral infections (Haerter et al., 2004) and appears to *inhibit virus replication*. A TNF-a blocking agent like etanercept, an immunosuppressive drug, is able to block the pivotal role of TNF-a in the inflammatory response. In this context, Hung et al. (Hung et al., 2017) investigated the relationship between an etanercept therapy and coronary events. The data as obtained by the study of Hung et al. are viewed by the **Table 4**.

Table 4. The study of Hung et al. 2017

		Coronary heart disease <B>		
		Yes	No	Total
Etanercept <A>	Yes	**2**	54	56
	No	1251	4953	6204
	Total	1253	5007	6260

k = -0,03904721
p value (k) = **0,00200547**

<A> EXCLUDES <B> and vice versa
p(EXCL)= 0,999680511
X^2(EXCL)= **0,04197426**

According to the data of the study of Hung et al. (Hung et al. 2017) with a sample size of N = 6260, we accept the Null-hypothesis: coronary heart diseae (CAD) and an etanaercept therapy are excluding each other (X^2(Excl) = 0.04, k= -0.03, p value(k) = 0.002) with the consequence that etanercept is a highly effective antidot against CAD (Hui-Yuen et al., 2006; Choueiter et al., 2010). **Q.e.d.**

Based on the data of Hung et al. (Hung et al. 2017), etanercept is highly effective against CAD. CAD itself is caused by HCVM (Barukčć, 2018d). *Conclusio*. Etanercept is highly effective against HCMV. Glioblastoma multiforme is caused by HCVM. Therefore, it is more than justified to considered etanercept for the therapy of glioblastoma multiforme.
Anti-tumor necrosis factor alpha (anti-TNF- alpha) antibodies are widely used to treat several inflammatory diseases and the treatment with a TNFalpha antagonist seems to be associated with various adverse (Bongartz et. al., 2006) events. Petersen at al. (Petersen et al., 2008) reported the history of a 37-year-old male who developed a primary HCMV infection following a month of therapy with etanercept 50mg twice weekly. After discontinuation of etanercept, the patient recovered. Six months later, the same patient restarted on etanercept without HCMV reactivation. This increasingly highlights the importance to stress out *the nature of coincidence of events*. The coincidence of an etanercept therapy and a new HCVM infection does not proof a causal relationship between both. Justification: After discontinuation of the therapy with etanercept, the same patient restarted on etanercept *without* (Petersen et al., 2008) reactivating a HCMV infection. Still, due to Petersen's case (Petersen et al., 2008) the question is justified, whether etanercept's property to control a HCMV infection is dose dependent.

3.3. Leflunomide is effective against HCMV

Leflunomide (N-(4'-trifluoromethylphenyl)-5-methylisoxazole-4-carboxamide) introduced for the treatment of rheumatoid arthritis in 1998 is an inhibitor of protein kinase activity and pyrimidine synthesis. Leflunomide with its antiviral properties (Teschner et al., 2010) appears not to inhibit viral DNA synthesis but rather seems to interfere with *virion assembly* (Sudarsanam et al., 2006). Leflunomide as an inhibitor of protein kinase activity and pyrimidine synthesis is an immunosuppressive agent which is effective against CMV (Waldman et al., 1999; John et al., 2004; Sudarsanam et al., 2006; Verkaik et al., 2013; Lu et al., 2015). Cytomegalovirus (CMV) itself is a major cause of mortality especially among pharmacologically immunosuppressed transplant recipients. Furthermore, HCMV is the cause of CAD (Barukčć, 2018d). An anti-CMV drug like leflunomide should be able to decrease coronary artery disease events like acute myocardial infarction.

Claims.
Null hypothesis:
Leflunomide and acute myocardial infarction are excluding each other.

Alternative hypothesis:
Leflunomide and acute myocardial infarction are not excluding each other. .
The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.
Suissa et al. (Suissa et al., 2006) investigated whether the risk of acute myocardial infarction (AMI) is associated with several disease-modifying antirheumatic drugs (DMARDs) commonly used in rheumatoid arthritis (RA) therapy including leflunomide. The data as obtained by Suissa et al. are viewed by the **Table 5**.

Table 5. The study of Suissa et al., 2006

		Acute myocardial infarction <B>		
		Yes	No	Total
Leflunomide <A>	Yes	**6**	194	200
	No	552	5386	5938
	Total	558	5580	6138

k = -0,03888389
p value (k) = **0,0023162**

<A> EXCLUDES <B> and vice versa
p(EXCL)= 0,999022483
X^2(EXCL)= **0,20546147**

According to the study of Suissa et al. (Suissa et al., 2006) with a sample size of N = 6138, we accept the Null-hypothesis. Leflunomide and acute myocardial infarction (AMI) are excluding each other (X^2(Excl) = 0.2, k=-0.03, p value(k) = 0.002). **Q. e. d.**

Suissa et al. (Suissa et al., 2006) were able to provide evidence that the use of leflunomide is associated with a reduction in AMI in patients with RA while AMI (i. e. CAD) itself is caused by HCVM (Barukčć, 2018d). *Conclusio*. Leflunomide is highly effective against HCMV (Waldman et al., 1999; Sudarsanam et al., 2006; Verkaik et al., 2013; Lu et al., 2015). Glioblastoma multiforme is caused by HCVM. Therefore, to date it is more than necessary that leflunomide becomes part of a therapy against glioblastoma multiforme.

3.4. Etoricoxib is effective against HCMV.

Etoricoxib is an anti-rheumatic drug used to help to control the inflammatory process in rheumatoid arthritis. Etoricoxib can be associated with an increased or decreased risk of coronary artery disease (CAD) in rheumatoid arthritis (RA) patients.

Claims.

Null hypothesis:

Etoricoxib and coronary artery disease (CAD) are excluding each other.

Alternative hypothesis:

Etoricoxib and coronary artery disease (CAD) are not excluding each other.

The significance level (Alpha) below which the null hypothesis will be rejected is alpha=0,05.

Proof.

Hung et al. (Hung et al., 2017) investigated whether an anti-rheumatic drug like etoricoxib is associated with an increased risk of coronary artery disease (CAD) in rheumatoid arthritis (RA) patients. The data of the study of Hung et al. are viewed by the **Table 6**.

Table 6. The study of Hung et al. 2017

		CAD <B>		
		Yes	No	Total
Etoricoxib <A>	Yes	**12**	144	156
	No	1241	4863	6104
	Total	1253	5007	6260

k = -0,04923852

p value (k) = **9,7891E-05**

<A> EXCLUDES <B> and vice versa

p(EXCL)= 0,998083067

X^2(EXCL)= **0,9533031**

The use of etoricoxib and CAD are excluding each other. The study of Hung et al. (Hung et al., 2017) with a sample size of N = 6260 provided significant evidence that etoricoxib is effective against CAD. We accept the Null-hypothesis: Etoricoxib and coronary artery disease (CAD) are excluding each other (X^2(Excl) = 0,9533031, k = -0.04, p value = 9,7891E-05). **Q.e.d.**

Based on the data of Hung et al. (Hung et al. 2017), etoricoxib is an anti-dot and effective against CAD. CAD itself is caused by HCVM (Barukčć, 2018d). *Conclusio*. Etoricoxib is effective against HCMV. Glioblastoma multiforme is caused by HCVM. Therefore, etoricoxib is of use for the therapy of glioblastoma multiforme.

4. Discussion

The growing need for medical knowledge based on evidence is generated an increasing medical literature supported by insufficient statistic methods (i. e. risk ratio) which many times provided seemingly contradictory results. In point of fact, many current published research findings and probably most of the conclusions drawn from biomedical research are probably false (Ioannidis, 2005). There is increasing concern about such an unreliable, inefficient and wasteful research is one fundamental reason for the non-deniable scepticism in the medical and non-medical community. Many times authors focus on one major aspect of this problem, the low statistical power (Button et al., 2103). In general, it is assumed that a study with low statistical power is inappropriate of detecting a true effect which leads to low reproducibility of results and the production of unreliable findings in studies. The size of the sample studied (Biau et al., 2008; Faber et al., 2014) may have a major influence on research outcomes and the interpretation of medical research. Inappropriate and inconsistent statistical methods used to analyse raw data are more responsible for this problem. Thus far, a key priority requires attention to review the 'well-established' but often insufficient methodological principles used to analyse data. Samples which are either too big or too small can compromise the conclusions drawn from a study. A sample which is too large may amplify the detection of differences whereas a small a sample may prevent the finding of differences.

The sample size of the studies analysed is very small but the studies are highly precise and have used the polymerase chain reaction technology to achieve some knowledge. As a consequence, the data are appropriate for a re-analyses.

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5. Conclusion

Human cytomegalovirus is the cause of IgA Nephropathy.

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