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Valaciclovir and/or Coriolus Versicolor Decreases the Risk of Transformation of Asymptomatic Monoclonal Gammapathies into Proliferative Disorders

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Abstract

Background: Monoclonal gammopathy of undetermined significance (MGUS) may develop into proliferative disorders.

Objective: Assess whether antiviral therapy (valaciclovir and/or Coriolus versicolor) may limit such transformations.

Methods: All relevant data were collected about patients presenting with MGUS, followed from at least 5 years and treated for at least 2 years with antiviral therapy. The observed evolution was compared to historical data regarding the occurrence of multiple myeloma, Waldenstrom's macroglobulinemia, primary amyloidosis or lymphoproliferative disorders.

Results: 21 patients were included. The global follow-up cumulates 233 patients-years. No case of transformation was reported.

According to historical data, 3 cases of transformation should have occurred ($p<0.05$).

In addition, MGUS disappeared in 6 cases whilst none was expected according to historical data ($p<0.01$)

Conclusion: We concluded that antiviral therapy (valaciclovir and/or Coriolus) may decrease the risk of MGUS progression to proliferative disorders.

Keywords: MGUS; herpes; valaciclovir; Coriolus

List of Abbreviations: CV: Coriolus versicolor; CMV: cytomegalovirus; EBV: Epstein-Barr Virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HPV: Human Papillomavirus; HSV: herpes simplex virus; MGUS: Monoclonal gammopathy of undetermined significance

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) may develop into proliferative disorders including myeloma or lymphoma [1].

Subsets of MGUS present with a monoclonal immunoglobulin specific for hepatitis B or C virus (HBV, HCV), thus are presumably HBV or HCV-driven, and antiviral treatment can lead to the disappearance of antigen stimulation and therefore can improve the control of clonal plasma cells [2].

The same may be true for Helicobacter pylori infection [3].

Epstein-Barr Virus (EBV) or cytomegalovirus (CMV) may also be implicated in the progression of myeloma or lymphoma [4].

However, to our knowledge, the effect of long-term anti-herpetic therapy on the risk of transformation of MUGS has not yet been evaluated.

Valaciclovir belongs to the standard treatments and prophylactic agents for infections caused by herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus [5].

Coriolus versicolor (CV) is efficacious against papillomaviruses (HPV) [6], and perhaps against HSV [7] or EBV reactivation [8]. CV may also decrease the risk of herpetic or SARS-Cov-2 infection [9].

Animal experiments confirmed that CV possesses anti-CMV properties [10].We investigated whether a long-term treatment with valaciclovir and/or CV was able to reduce the occurrence of transformation of MGUS.

Material and Methods

This work is a descriptive retrospective epidemiological study.

Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth, from 2005 September 1st to 2024 July 30th.There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before data collection. This retrospective analysis of Case Series cannot therefore be qualified as “research” and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE). French legislation does not require the consent of an Institutional Review Board in such epidemiological studies.

Inclusion Criteria

All patients who were diagnosed with MGUS and who received any long-lasting anti-viral treatment (at least 3 years) were included. Only patients followed more than 5 years were included. Patients with chronic herpetic flares received valaciclovir. Patients with adenocarcinoma or HPV received CV.

Patients signed a written consent for the possible retrospective use of the anonymized collected data.

Exclusion Criteria

Lack of signed consent for possible retrospective epidemiological use of data; incomplete information on CMV-serology or EBV-serology.

Statistics

No case was discarded except when at least one exclusion criteria was identified. As a consequence no recruitment or selection bias is expected. All patients were Caucasian.Because of the very small number of theoretical (historical/calculated/expected) or observed cases, we used the Poisson distribution to compare the two groups.

Historical Group

The number of expected cases of transformation was calculated according to the data published by Kyle RA et al [1]. This historical cohort consists of 1,384 patients and the monitoring covers up to 25 years. The percentages of transformation appear therefore reliable.

The historical group enables to calculate the expected rate of transformation for each patient according to the duration of the follow-up and of other risks criteria (namely the concentration of M protein, IgA type or IgM type).

The rate of transformation was summed up for the 21 patients in order to obtain the theoretical (calculated = expected) number of transformed cases.

The theoretical number was compared to the observed one.

Age appears to be comparable in the observed and in the historical group (63 years versus 64). Female patients were more numerous in the observed cohort (66.7% versus only 42.0% in the historical group). However, these two parameters are not expected to have any impact on the transformation rate of MGUS.

The rate of spontaneous disappearance of MGUS is very low (20/618 =0.3% [11]). The theoretical number of patients with spontaneous disappearance of MGUS in a cohort of 21 patients can therefore be rounded to zero (21 x 0.3%).

Results

The observed group (see table 1)

This descriptive observational epidemiological study includes 21 patients.

No patient with MGUS was excluded since all required data were available, especially regarding CMV or EBV serology. There is therefore, no exclusion effect.

According to inclusion criteria, all patients received valaciclovir and/or CV.

Valaciclovir was given for chronic herpetic flares (15 patients) and CV was given for HPV infection (4 cases), cancer (3 cases) or chronic herpetic infection (15 cases). Valaciclovir was associated with CV in 15 cases. CV was given alone in 6 cases. Valaciclovir was never given alone.

All patients were followed-up for at least five years and were treated for at least 2 years.

All patients were Caucasian. No patient had a medical history of hepatitis B or C. No patient received any antitumor therapy.The age ranged from 50 to 85 years. The median age of patients was 63. Two third of patients were women. All were IgG-EBV+ and Helicobacter negative – according to serologic or gastroscopic results.

The M protein was IgG κ for 14 patients, IgG λ for 3 patients, IgM κ for 1 patient, IgM λ for 1 patient, IgA κ for one patient and IgA λ for the last patient.Only one patient presented with a high level of M-protein.

The follow-up period ranged from 5 to 19 years with a median of 10 years. The cumulated follow-up for the 21 patients was 233 patients-years.

15 patients presented with chronic herpetic flares when the antiviral therapy was initiated. 2 patients had a medical history of zona, 11 patients had a positive IgG-serology against CMV and 4 patients had a medical history of clinical HPV-infection.

During the follow-up, all chronic herpetic flares were controlled by the anti-viral therapy. No zona was reported and no recurrence of CMV or HPV infection. Cancers remained in remission.

At the end of the follow-up no case of transformation was reported. The M-protein level increased in one case, was stable in 11 patients and decreased in 6 cases. M-protein disappeared in 6 patients.

Table 1: Demographic data and details of MGUS, treatment type and evolution per patient

Patients	Age*	Gender	Type of MGUS and serum level at diagnosis in g/dl	Follow-up in years	Type of antiviral therapy and duration** in years	Medical history of				Risk of transformation according to the historical group***	Evolution of the M protein in g/dl
						chronicHerpes simplex flares	Zona	IgG CMV +	HPV		
1	61	F	IgG κ (0.5)	6	valaciclovir + CV3	+	+	+	-	6%	0.5 stable
2	70	F	IgG λ (0.59)	19	CV(HPV)14	-	-	+	+	20%	0.33 Decrease>20%
3	60	F	IgG κ (0.74)	18	CV(HPV)3	-	-	-	+	19%	0.54 Decrease>20%
4	64	F	IgM κ (0.4)	9	valaciclovir + CV6	+	-	-	-	18% (risk factor)	0.31 Decrease>20%
5	52	M	IgG κ (3.23)	12	valaciclovir+ CV3	+	-	+	-	52% (severe risk factor)	3.3 Stable
6	67	M	IgG κ (0.71)	7	valaciclovir+ CV2	+	-	+	-	7%	0 disappearance
7	57	F	IgG κ (0.5)	10	valaciclovir+ CV4	+	-	-	-	10%	0 Disappearance
8	51	M	IgG κ (0.24)	14	valaciclovir+ CV2	+	-	+	-	14%	0.28 Stable
9	73	M	IgM λ (0.31)	6	valaciclovir+ CV2	+	-	-	-	12% (risk factor)	0.34 Stable
10	63	F	IgG λ (0.56)	10	valaciclovir+ CV3	+	-	+	-	10%	0.51 Stable
11	54	M	IgG κ (0.20)	15	valaciclovir+ CV4	+	-	+	-	15%	0 Disappearance
12	85	M	IgG λ (0.15)	15	CV(prostatic cancer)3	-	-	+	-	15%	0 Disappearance
13	58	M	IgA κ (0.58)	11	valaciclovir + CV(colonic cancer)	+	-	-	-	22% (risk factor)	0 Disappearance

14	68	F	IgG κ (0.6)	8	CV(breast cancer)4	-	-	+	-	8%	0.6 Stable
15	73	F	IgA λ (0.50)	16	valaciclovir+ CV5	+	-	+	-	32% (risk factor)	0 Disappearance
16	53	F	IgG λ (0.60)	12	valaciclovir+ CV3	+	-	-	-	12%	0.67 Stable
17	72	F	IgG κ (0.67)	7	CV(HPV)4	-	-	+	+	7%	0.88 Increase
18	50	F	IgG κ (0.37)	5	valaciclovir+ CV2	+	+	+	-	5%	0.35 Stable
19	60	F	IgG κ (0.18)	10	CV(HPV)2	-	-	-	+	10%	0.2 stable
20	62	F	IgG κ (0.16)	10	valaciclovir+ CV2	+	-	-	-	10%	0.17 Stable
21	83	F	IgG κ (0.26)	6	valaciclovir+ CV3	+	-	-	-	6%	0.3 Stable
Total21	50 to 85Median = 63	14 female7 male	IgG κ = 14 IgG λ = 3 IgM κ = 1 IgM λ = 1 IgA κ = 1 IgA λ = 1 Only 1 >3 g/dl	Median = 10Total follow-up = 233 patient-years	valaciclovir+ CV(15 cases)CV alone (6 cases)	15	2	11	4	3, 1 ExpectedTransformed cases↓ 0 expected disappearance of MGUS §	0 observed transformed cases Increase=1 Stable = 11 Decrease = 3 Disappearance = 6

*At the end of the follow-up (2024 July 30th)**The treatment is still ongoing at the end of the follow-up*** Calculated according to the duration of follow-up and type of M protein (increased risk of transformation when IgM type or IgA type) [1]

19 out of 21 patients presented with either chronic herpetic flares (all labial; 15 cases) or a medical history of clinical HPV infection (4 cases). All patients were IgG-EBV + and Helicobacter pylori negative.

↓p<0.05; § p<0.01

The historical group (see table 1; 11th column)

The median age was 64 years, patients were mainly male (58%) and were not all Caucasian.

Transformation rate of MGUS was approximately 1% per year. Risk factors were IgM, IGA (approximately doubled risk) or the high level of serum M-protein (52% at 12 years of follow-up).

No disappearance of M-protein was reported.

The calculated risk of transformation was calculated for each patient according to the duration of the follow-up, the type of M-protein and its serum concentration.

The sum of the theoretical risk of transformation for the 21 patients of the observational group was 3.1, rounded to 3.

It means that 3 cases of transformation should have been reported in our cohort of 21 patients if the rate of transformation from the Kyle's study would be applied.

Therefore, we compared 0 reported case to 3 theoretical occurrences with Poisson's distribution ($p<0.05$).

We also compared the 6 reported cases of disappearance of the M-protein to number of calculated disappearance, namely none ($p<0.01$).

We concluded that the applied long term antiviral therapy decreased the risk of transformation of MGUS.

Discussion

MGUS is a spectrum of disorders characterised by clonal proliferation of plasma cells or lymphocyte B [12].

CMV, EBV or HPV may drive transformation or mediate immune escape

The mechanism of transformation of lymphocyte B may be the integration of the virus close to genes of immortality as suggested by Gulbahce N et al [13], especially for EBV and HPV.

EBV is strongly associated with a large spectrum of lymphoproliferative diseases. EBV expresses latent viral proteins which promote survival of tumor cells. Several FDA-approved drugs can kill some of the EBV-induced lymphoproliferative cells by inhibiting the function of latent viral proteins [14].

Although EBV latency is assumed to be necessary for oncogenic transformation, the initiation of the lytic cycle has now been shown to support EBV-driven malignancies. The replication of EBV is therefore necessary for tumorigenesis. In addition, non--coding RNAs might mediate immune escape and contribute to viral persistence. Early lytic EBV antigens and non-coding microRNAs could be harnessed with antiviral or immunotherapies in order to control transformation [15].

CMV is an immensely pervasive herpesvirus, developing multiple immune-modulatory strategies. CMV evades immune cells mainly through maintaining its viral genome, impairing HLA Class I and II molecule expression, dampening natural killer cytotoxicity, interfering with cellular signaling, inhibiting apoptosis, escaping complement attack, and stimulating immunosuppressive cytokines. CMV expresses several gene products that modulate the host immune response and promote modifications in non-coding RNA and regulatory proteins. Hence, tumor survival is promoted by affecting cellular proliferation and survival, invasion, immune evasion, immunosuppression, and giving rise to angiogenic factors [16].

HPV is associated with the development of different types of cancer, such as cervical, head and neck (including oral, laryngeal, and oropharyngeal), vulvar, vaginal, penile, and anal cancers. The integration of HPV genome into host cell chromosomes and genes induces the loss of function of tumor suppressor genes and increases oncogene expression. The viral genotype, infection with multiple viruses, viral load, viral persistence, determine the viral breakage pattern and the sites at which the virus integrates into the host cell genome (introns, exons, intergenic regions), especially those close to p53 [17]. The HPV-oncoprotein E7 may also induce epigenetic silencing of host innate immunity [18].

As a consequence it may be speculated that any intervention which may control the proliferation of those viruses or their integration into the human genome may block the transformation of MGUS or decrease the dampening of innate immunity.

Valaciclovir or CV controls viral replication and reduces immune evasion

The transformation rate of MGUS into myeloma or lymphoma could be reduced by antiviral therapy: against viral hepatitis [2] or, according to our work, against herpes viruses. Valaciclovir may therefore be proposed to patients as well as CV.

Aciclovir and derivatives are viral DNA polymerase inhibitors of HSV and remain the gold standard treatment of these infections despite a problem of resistance [19, 20].They are also partly efficacious against CMV primo-infections or recurrences [21,22] and even EBV [23].

CV is currently successfully used in humans against HPV [6] or herpetic infections [7-9]. CV also possesses immunostimulat-

ing [24] and antitumor properties [25, 26].

CV's glycoproteins and polysaccharopeptide may arrest different phases of the cell cycle, stimulate immunity, induce apoptosis, reduce BCL-2 expression or increase the expression of p53 tumour suppressor genes [27].

Neither aciclovir nor CV is expected to inhibit viral DNA integration.

Curcumin has also been successfully used in MGUS [28]. It inhibits the proliferation and induces apoptosis of multiple myeloma cells through the downregulation of IL-6 and NF-kB [29].

Lectins (such as rice bran and Shiitake) may increase the efficacy of curcumin against MGUS transformation [30]. The suggested mechanisms of their action were immunostimulation and direct pro-apoptotic effects against myeloma cells [31].

According to experimental animal data on plasmocytoma cells, the effect CV-lectins – named PSK – is expected to at least mimic the effect of rice bran and Shiitake [32].

Limitations of the Study

The retrospective design of the study precludes any causal relationship conclusion.

All patients were Caucasian which may limit our conclusion to this population. The prevalence of MGUS is 3.0-fold higher in African-Americans than in whites [33] and is lower in Japanese patients [34]. However, ethnicity is not a risk factor of transformation [1]. Our conclusion – which only concerns transformation – could therefore probably be applied to all patients with MGUS, regardless of gender or ethnicity.

Populations were not randomized and the two groups may be different, leading to some biases. However the observed group and the historical group appear similar with regard to the risk of transformation.

All patients with MGUS, with a long-term follow-up and with a long-term antiviral therapy were included. All risk factors and chronic viral infections were taken into consideration. However, unknown biases may still remain and alter our conclusions.

Application of this new knowledge for routine practice. In practice, valaciclovir and CV are innocuous and inexpensive products. They may reduce the risk of herpetic flares which are implicated in Alzheimer disease [35], the risk of CMV recurrences, which are implicated in immunosenescence [36] and the risk of HPV infection, which is implicated in numerous cancers [37].

We suggest that patients with MGUS and herpetic or HPV infection receive valaciclovir +/-CV on a long term basis to avoid transformation. Curcumin may increase the positive results.

One may even go further and propose that, because of the good safety profile of valaciclovir, CV and curcumin, a preventive long-term therapy with these products could be offered to all patients with MGUS rather than a simple surveillance. Such prevention may also reduce diseases promoted by chronic HPV or herpetic infections.

Conclusion

Patients with MGUS and treated with valaciclovir +/- CV appears to experience less transformation into myeloma or lymphoma.

Studies should be performed to further investigate the interest of innocuous anti-viral therapy in the prevention of immortalisation of lymphocyte B.

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