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L'hépatite auto-immune à immunoglobulines G4: une nouvelle entité potentiellement présente dans les pays occidentaux

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UNIVERSITE DE NICE SOPHIA-ANTIPOLIS



FACULTE DE MEDECINE

L'HEPATITE AUTO-IMMUNE A IMMUNOGLOBULINES G 4 : UNE NOUVELLE ENTITE POTENTIELLEMENT PRESENTE DANS LES PAYS OCCIDENTAUX

Thèse de DOCTORAT en MEDECINE

(Diplôme d'Etat)

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Par

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Discipline : Hépatogastroentérologie

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IgG4 –associated autoimmune hepatitis: an new entity that may be present in Western countries

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This work was done in the Digestive Center of the “Centre hospitalier universitaire” of Nice, France.

Short title: IgG4-associated autoimmune hepatitis in Europe

List of abbreviations:

BMI: Body Mass Index

AST: ASpartate amino-Transferase

ALT: ALanine amino-Transferase

gGT: Gamma Glutamyl-Transferase

W: Women

M: Men

NS: Not Significant

Conflict of interest: Nothing to disclose.

Résumé :

Introduction : La maladie à Immunoglobuline (Ig) G4 est une maladie auto-immune systémique récemment découverte. L'atteinte isolée du foie a été rapportée chez des patients Japonais et porte le nom de "hépatite auto-immune (HAI) à IgG4". L'objectif de ce travail était d'étudier au moment du diagnostic et après un suivi de 2 ans les caractéristiques de patients présentant une HAI à IgG4 en comparaison à ceux présentant une HAI classique.

Méthode : Tous les patients présentaient une HAI caractérisée. Tous les patients avaient une biopsie du foie avant de débiter le traitement. Le traitement (corticoïdes ± aziathropine) des patients était donné en suivant les recommandations internationales. "L'HAI à IgG4" était définie selon les critères d'Umemura : présence d'au moins 10 plasmocytes marqués IgG4 en immuno-histo-chimie, dans un espace porte à fort grossissement.

Résultats : Parmi les 30 patients inclus (19H/11F, 51,1 [42-64,5] ans), 7 avaient une "HAI à IgG4" et 23 avaient une HAI classique. Dix (33%) patients présentaient une fibrose sévère ou une cirrhose, l'activité inflammatoire était sévère chez 13 (43,3%) patients. Le degré de fibrose et l'activité étaient similaires dans les 2 groupes (respectivement $p=0,27$ et $p=0,18$). Le niveau d'alanine amino transférase (ALAT) et le niveau sérique d'immunoglobuline G étaient similaires à l'admission, à 1 an et à 2 ans dans les 2 groupes. La réponse biochimique complète (définie par $ALAT < N$) était similaire entre les groupes HAI à IgG4 et HAI classique (67 versus 79% à 1 an, $p=NS$; 67 versus 63% à 2 ans, $p=NS$).

Conclusion : Des HAI à IgG4 pourraient exister aussi dans les pays occidentaux. L'évolution semble similaire à celle des HAI classiques. Des études prospectives sont nécessaires pour mieux caractériser cette entité et savoir s'il s'agit d'une maladie à part entière ou d'une variante des HAI classiques.

Abstract

Background and aims: Immunoglobulin (Ig) G4 related disease is a multi-systemic autoimmune disease. The sole involvement of the liver has been recently reported in Japanese patients and named the “IgG4-associated Autoimmune Hepatitis (AIH)”. The **aim** of this study was to examine the baseline and the 2-year follow-up characteristics of non-Asian patients with an “IgG4-associated AIH” compared to patients with a classical AIH.

Methods: All patients had a liver biopsy before starting any treatment. Treatment (steroid \pm azathioprine) of all patients was done according to international guidelines. “IgG4-associated AIH” was diagnosed according the Umemura’s definition: the presence of at least 10 positive IgG4-plasma cells in high power field centred on a portal tract.

Results: Among the 30 patients (19 W/11M, 51.1 [42-64.5] years): 7 had an “IgG4-associated AIH” and 23 had a classical AIH; 10 (33%) patients presented severe fibrosis or cirrhosis, the necro-inflammatory activity was severe in 13 (43.3%) patients. Fibrosis and activity were comparable between both groups (respectively $p=0.27$ and $p=0.18$). Alanine amino transferase (ALT) activity and serum immunoglobulin G level were similar at baseline, and at one year and two years between both groups. Complete biochemical responses (ALT < N) were similar between IgG4-associated and classical AIH (67 vs 79 % at one year, $p=NS$; 67 vs 63 % at two year, $p=NS$).

Conclusion: “IgG4-associated autoimmune hepatitis” could be observed in Western patients and seems to evolve similarly to classical AIH. More prospective studies are necessary to better characterize and manage this new entity.

Key words:

Autoimmune hepatitis

Immunoglobulin G 4

Plasma cells

Immunoglobulin G 4-associated autoimmune hepatitis

Key point box:

- IgG 4-associated autoimmune hepatitis may be a new disease
- IgG 4-associated autoimmune hepatitis has only been described in Japanese patients
- IgG4-associated autoimmune hepatitis may be also present in Western countries
- IgG4-associated autoimmune hepatitis may have the same response to treatment compared to classical autoimmune hepatitis

Introduction:

Autoimmune hepatitis (AIH) is a well-defined entity; however, its exact pathophysiology is still not well known. Its incidence varies geographically. The annual incidence of AIH in Europe is 0.8-1.9 cases per 100,000 with a prevalence of 11.6-17 per 100,000 people [1]. In Asia, most reports come from Japan, where AIH is considerably less frequent than in Western countries with an incidence estimated between 0.08 and 0.15 cases per 100,000 people per year [2]. Diagnostic criteria of AIH have been proposed through an international consensus [3]. AIH can be associated with other autoimmune diseases. In the liver, the most frequent associations (overlap syndrome) are with primary sclerosing cholangitis (PSC) and primary biliary cirrhosis (PBC) [4]. AIH treatment is based on steroid therapy is frequently associated with immunosuppressors such as azathioprine [1].

Recently, a new identified autoimmune family disease has been described and named "immunoglobulin G4 related diseases" (IgG4-RD) [5]. The main affected organs are pancreas, biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin [6]. Over the last decade, a number of diagnostic criteria for IgG4-RD have been published. For the diagnosis of autoimmune pancreatitis (AIP) the HISORt criteria from the Mayo Clinic have been retained [7,8]. These criteria take into account: Histology, medical Imaging, elevated serum IgG4 levels on Serological testing, Other organ involvement and Response to steroid therapy [7,8]. These criteria are defined only for AIP, but could probably be applied to other sites of IgG4-RD. The 4 hallmarks of IgG4-RD are: dense lymphoplasmacytic infiltrate with a high percentage of IgG4+ plasma cells (IgG4+cells >40% of all plasma cells or >10-50 IgG4+cells per high powered field-with a threshold dependent on organ involvement), storiform fibrosis, obliterative phlebitis and mild to moderate tissue eosinophilia. Elevated serum IgG4 levels (>135 mg/dL) may help in the diagnosis, but are not considered to be diagnostic. Studies of type 1 AIP estimated the prevalence of the serum IgG4 increase to be around 70 to 80% [9]. Yet, the epidemiology of IgG4-RD remains poorly described. The incidence and prevalence of IgG4-RD are probably substantially underestimated because recognition of this condition has begun to increase only within the past decade. In some cases, IgG4-RD can be located on one organ, particularly the pancreas. This is suspected to represent one of the type 1 autoimmune pancreatitis [10]. Recently, isolated liver damage with

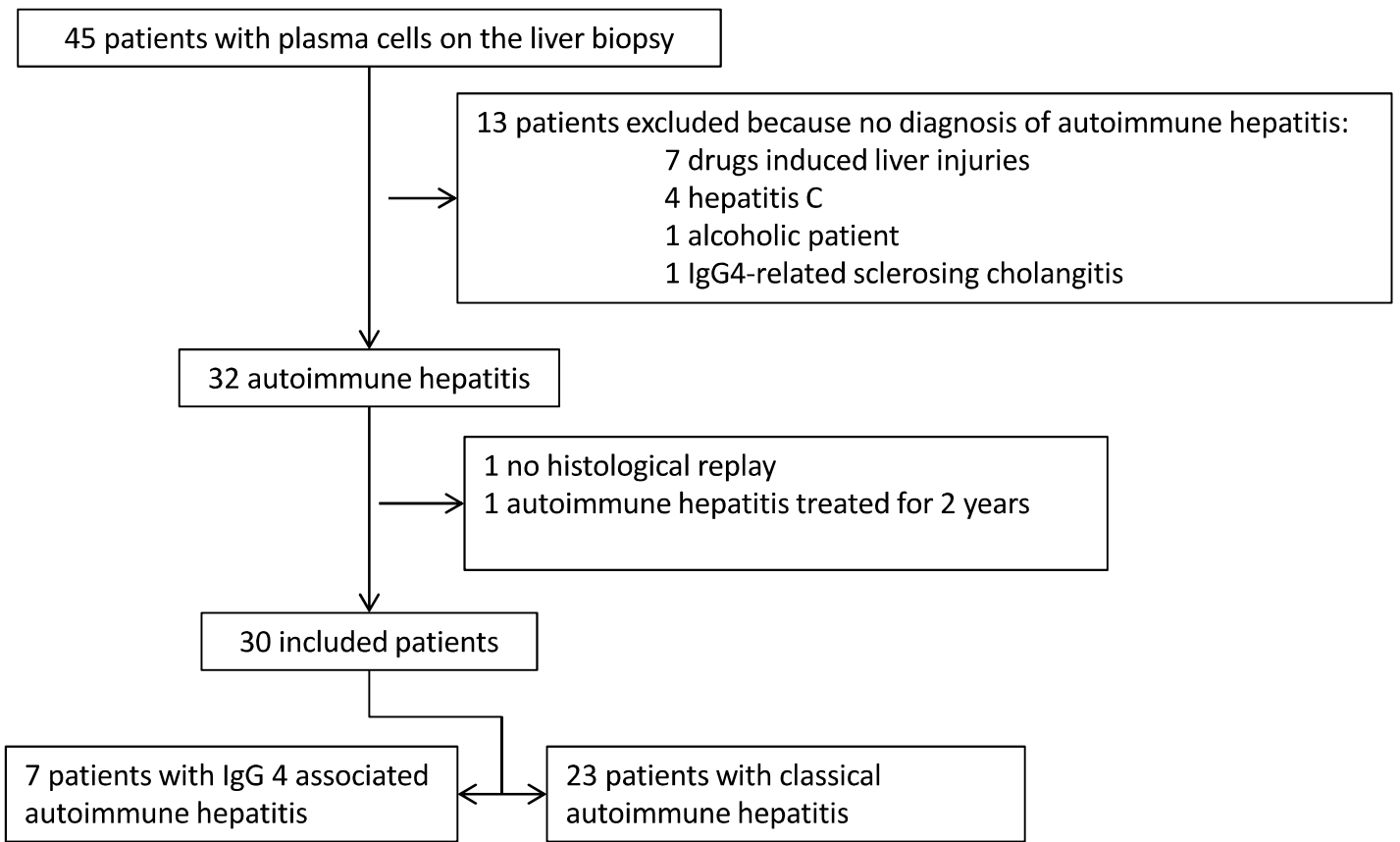
lymphoplasmocytic infiltrate and a high percentage of IgG4+ plasma cells has been reported in Japanese patients. This new entity has been named the IgG4-associated autoimmune hepatitis. Up until now, only few Japanese patients have been reported to have an IgG4-associated autoimmune hepatitis [11–13].

We hypothesized that IgG4-associated autoimmune hepatitis may also be present in European patients. The aim of this retrospective, pilot study was to examine the frequency, the characteristics and the 2 year follow-up of potential IgG4-associated autoimmune hepatitis among European patients newly diagnosed with AIH.

Patients and methods:

Patient selection design. Inclusion criteria were based on the liver biopsy. The selection mode of patients was based on software for archiving pathological reports (Apix, Apix technology, Grenoble, France). Among the 1885 liver biopsies performed in our hospital between January 2009 and December 2011, the patients included in this study were those whose plasma cells from liver biopsies had the Apix code (BHFF9400). Forty-five patients were consistent with this criterion (figure 1). Thirteen patients were excluded because of absence of AIH diagnosis (7 had drug induced liver injuries, 4 patients had hepatitis C, 1 had alcoholic liver disease, 1 had an IgG4 cholangitis). AIH diagnosis was confirmed if the patients had typical histology (portal/lobular inflammation with mononuclear and plasma cells and piecemeal necrosis) eventually associated with specific laboratory criteria (increased total gamma globulins and/or increased total serum Immunoglobulin G and/or anti-smooth muscle antibodies (SMAs)-actin specific- and/or anti-liver kidney microsomal antibody type 1 (LKM-1)). Simplified criteria for the diagnosis of AIH defined by Hennes et al. in 2008 were assessed for all patients, but were not used as inclusion criteria [14]. Among 32 patients with AIH, 2 were excluded: 1 had no histological replay and 1 had an autoimmune hepatitis already known and was treated for 2 years. All patients were followed up during 2 years. All patients had medical imaging (liver ultrasound or Magnetic Resonance Imaging) in order to assess the biliary tract and associated pancreatitis. All patients were separated into 2 groups according to the presence of IgG4 plasma cells in the biopsy. The control group was composed of patients with autoimmune hepatitis defined by less than 10 IgG4 plasma cells per high power field centered in the portal tract. This group, with 23 patients, was named in this article "classical AIH". The second group was composed of patients with AIH, having more than 10 IgG4 plasma cells per high power field centered in the portal tract. This group, with 7 patients, was named in this article "IgG4-associated AIH", the new entity. The study protocol was performed according to French legislation regarding Ethics and Human Research and was conformed to the Declaration of Helsinki. Written informed consent was obtained from all patients.

Figure 1: flow chart of the patients



IgG: immunoglobuline

Methods:

Patient characteristics

Clinical and biological data were collected at baseline, at 1 year and at 2 years including: age, sex, body mass index (BMI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, gamma glutamyl transferase (gGT), plasma immunoglobulin G, gamma globulin, antibody titre (anti-nuclear (ANA) and/or anti-smooth muscle antibodies (SMAs) and/or anti-liver kidney microsomal antibody type 1 (LKM-1)). We had no data about IgG4 serum level. Data from treatment with doses of corticosteroids and immune-suppressive therapy were collected at baseline, at 1 and 2 years.

For all patients, exhaustive clinic-biological investigations had been performed prior to the realization of the liver biopsy, in order to justify the liver abnormalities. This included clinical and biological assessment in order to exclude excessive alcohol consumption, serologies for hepatitis B and C, hemochromatosis, Wilson disease, alpha 1 anti-trypsin deficiency, non-alcoholic fatty liver disease.

In order to characterize overlap syndrome between AIH and primary biliary cirrhosis, anti-mitochondria M2 antibody, serum level of IgM and specific liver pathological lesion compatible with primary biliary cirrhosis were systematically assessed.

Pathological examination

All liver biopsies, except one, were obtained percutaneously with an 18 Gauge needle under ultrasound guidance. One histological analysis was obtained on a liver explant after a liver transplantation. All liver biopsies were taken before administration of corticosteroid treatment and were reviewed by one liver pathologist (SP) blinded from the clinical or biological characteristics of the patients. Formalin-fixed and paraffin-embedded specimens were prepared and used for histopathological and immunocytochemistry studies. Liver biopsies were processed routinely and stained with hematoxylin-eosin-safran and Sirius Red. The quality of biopsies was sufficient for interpretation. The lengths of the liver biopsies were over 15 mm and each contained 3 to 25 portal tracts.

Autoimmune hepatitis was assessed according to criteria by Alvarez et al. [3].

Briefly, the grade of the necro-inflammatory activity score was assessed as follows: 0, no activity; 1, mild activity; 2, moderate activity; 3, severe activity. Fibrosis was

assessed as follows: 0, no fibrosis; 1, mild fibrosis; 2, bridging fibrosis; 3, severe fibrosis; 4, cirrhosis.

Immunocytochemistry for IgG4 were realized for all liver biopsies. Immunostaining for IgG4 was performed using mice monoclonal antibodies against human IgG4. Sections measuring 2 μm were cut from each paraffin block and were put to dry at 37°C during 12 hours. After deparaffinization and rehydration, all sections were pretreated at pH6 with Flex TRS Low (PTLink DAKO, Glostrup, Denmark) during 20 minutes. Endogenous peroxidase was blocked in 1% hydrogen peroxide for 5 minutes (DAKO, Glostrup, Denmark) at room temperature. After rinsing with phosphate buffered saline, the sections were incubated with a monoclonal antibody to IgG4 (clone HP6025 Life Technology, Waltham, MA, USA) at dilution 1:100 for 20 minutes at room temperature. Then sections were incubated with an appropriate biotinylated secondary antibody from the Envision flex/HRP Mouse/Rabbit kit (Dako, Glostrup, Denmark) for 20 minutes, at room temperature. Next, slides were incubated in PBS, for 20 minutes, at room temperature, and then peroxidase activity was detected by diaminobenzidine tetrahydrochloride for 8 minutes and used for visualization and haematoxylin (Dako, Glostrup, Denmark) during 5 minutes for nuclear counterstaining.

The number of cytoplasmic stainings was counted with each high power field centered on a portal tract (magnification x400). IgG4-associated autoimmune hepatitis was defined histologically using the criteria proposed by Umemura: presence of at least 10 positives IgG4 plasma cells in high power field centred on a portal tract [15].

Statistical analysis: Quantitative variables are presented as the median and 25th-75th interquartile range. Qualitative variables are presented in percentage. Comparisons between patients with and without IgG4-associated autoimmune hepatitis according to Umemura were realized at baseline, 1 and 2 years of follow-up. Quantitative values were compared using T test or non-parametric Mann-Whitney test as requested. Qualitative variables were compared using Chi2 test. A logistic regression was realized in order to find independent parameters associated with IgG4-associated autoimmune hepatitis. The parameters included in the logistic regression analysis included significant and relevant ones avoiding redundancies. All calculations were made using NCSS 2007 (Saugus MA 01906, U.S.A.).

Results:

1) Epidemiological characteristics of the study population

Thirty patients (19 women (W)/ 11 men (M)) were included in our study (Table 1). Seven (23%) patients came from North-Africa and 23 (77%) were Caucasian. The median age was 51.1 [42-64.5] years. Median serum IgG concentrations were 25.4 [17.68-32.48] g/l.

Twenty-six (87%) patients presented probable or definite AIH (score ≥ 6) according to the simplified international criteria [14]. Three (10%) patients had a score of 5: two had antibody negatives; one had normal concentration plasma cells. This patient died of a fulminant hepatitis. Liver biopsy found mainly necrosis, which could explain the absence of histological evidence of autoimmune hepatitis. However, in the portal tract, plasma cells were found in moderate numbers. All patients with IgG4-associated AIH presented a simplified international criteria score ≥ 6 (p=NS). Two patients were under 18 (14 and 15 years old): one had type 1 AIH and the other had type 2 AIH. Both were IgG4 negative.

Histological results for the whole cohort were: Fibrosis (F)1 : 53.3%, F2 :13%, F3 :10%, F4 :23,3% and Activity (A)1 :16,6%, A2 :40%, A3 :43,3%.

All patients had MRI or ultrasonography to assess the liver, the pancreas and the biliary tract. One patient, IgG4-associated AIH, had a PSC. No patient had associated pancreatitis.

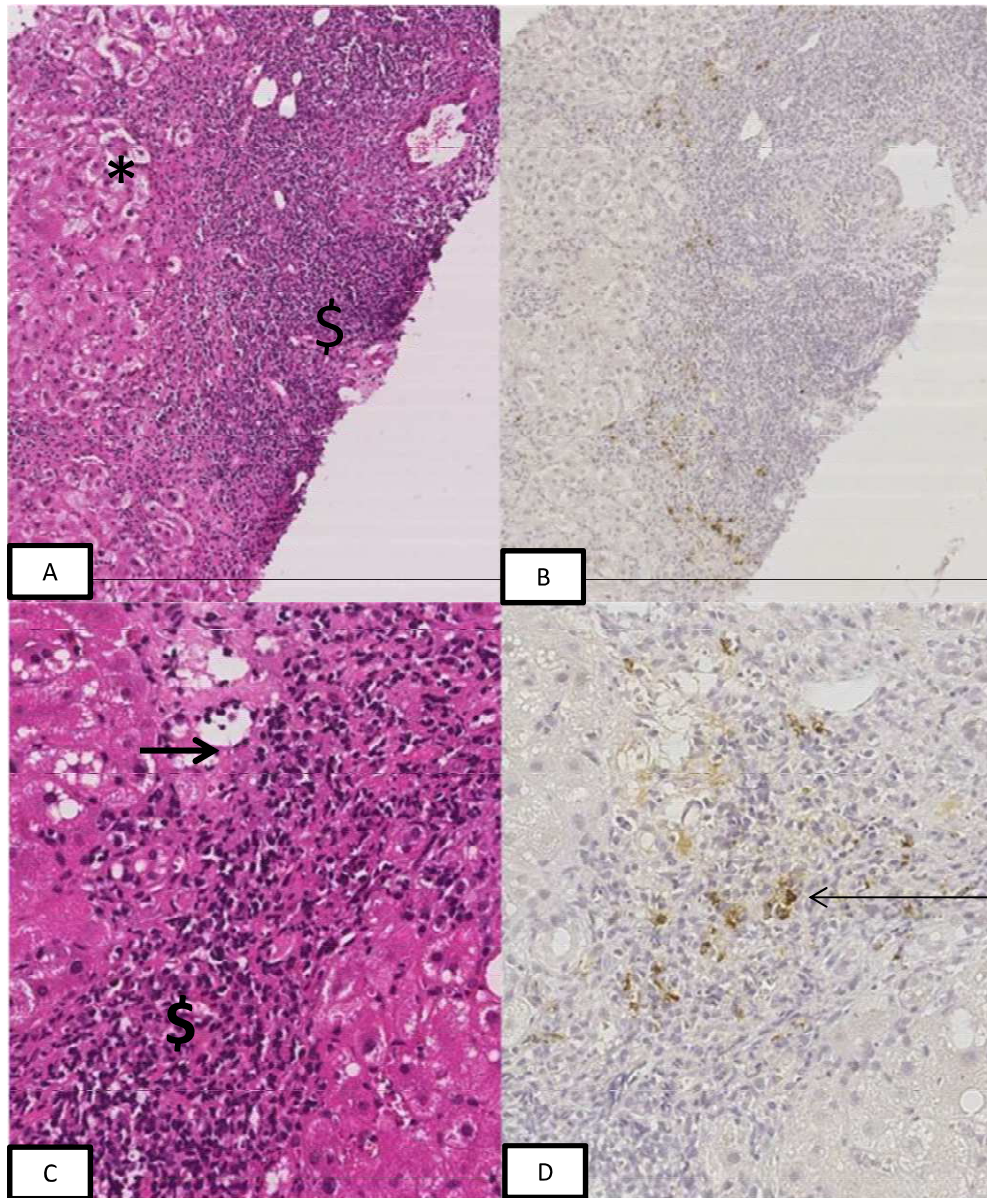
Seven patients were IgG4 positives according to Umemura's criteria and are designed as patients with an "IgG4-associated autoimmune hepatitis" (figure 2 and 3).

Table 1: characteristics of all the population at baseline

Variable	Data at baseline median [interquartile range]
Number of patients	30
Sex (Female)	19
Age (year)	51.1 [42-64.5]
BMI (kg/m ²)	24.3 [21.8-26.1]
ASAT (IU/l)	582 [219.7-1129.5]
ALAT (IU/l)	708.5 [205.5-1569.5]
Gamma GT (IU/l)	174.5 [119-371]
Alkaline phosphatase (IU/l)	180 [109.2-252]
Total bilirubin (µmol/l)	34.5 [17-201.7]
Conjugated bilirubin (µmol/l)	23 [6.25-154]
Gamma globulin (IU/l)	23.6 [16.1-30.4]
Total plasma IgG (g/l)	25.4 [17.7-32.5]
IgG 4-associated autoimmune hepatitis according to Umemura n (%)	7 (23.3 %)
Overlap syndrom n (%)	2 (6 %)
Fibrosis F1 n (%)	16 (53.3 %)
Fibrosis F2 n (%)	4 (13 %)
Fibrosis F3 n (%)	3 (10 %)
Fibrosis F4 n (%)	7 (23.3 %)
Inflammation A1 n (%)	5 (16.7 %)
Inflammation A2 n (%)	12 (40 %)
Inflammation A3 n (%)	13 (43.3 %)

Quantitative variables are presented as the median and 25th-75th interquartile range. BMI = body mass index; ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase; Gamma GT = gamma glutamyl transferase; IgG = immunoglobulin G

Figure 2: One liver biopsy of IgG4-associated AIH with HES and IgG4 IHC.

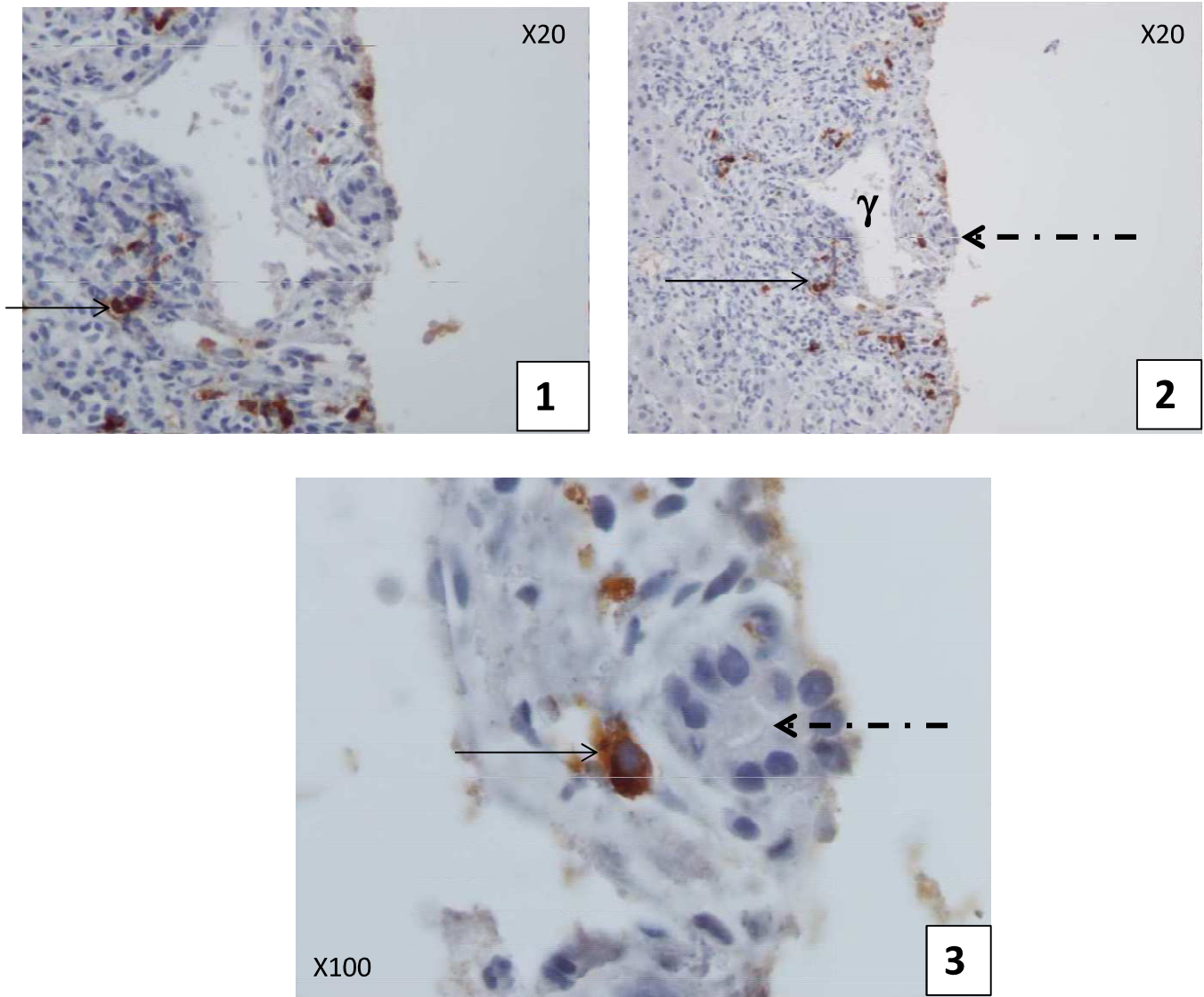


Panel A HESx10: Dense inflammatory infiltrate (\$) in fiber spans, enclosing hepatocyte nodules (*)

Panel C HESx40: Infiltrate composed of mononuclear cells (lymphocytes, plasma cells) (\$) and attacks the bordante hepatocyte blade (→)

Panel B and D IHC anti IgG4: This infiltrate contains positive IgG4 plasma cells (→) (cytoplasmic staining)

Figure 3: One liver biopsy of IgG4-associated AIH with immunocytochemistry for IgG4



Panel 1 , 2 and 3 : These infiltrates contain positive igG4 plasma cells (→).
 γ = vein ; $\leftarrow \cdot \cdot \cdot$ = biliary duct ;

2) Comparison between patients with and without IgG4-associated autoimmune hepatitis at baseline

Gender (4W/3M versus (vs) 15W/8M $p=NS$), median age (49 [42-67] vs 54 [42-64] years, $p=NS$) and ethnic group (2 North African/5 Caucasians vs 5 North African/18 Caucasians, $p=NS$) were similar between patients with and without IgG4-associated autoimmune hepatitis, respectively.

The grade of the activity and the stage of the fibrosis were similar between patients with and without IgG4-associated autoimmune hepatitis.

Anti-smooth-muscle antibody (6 vs 30, $p=NS$) and anti-nuclear antibody (4 vs 11, $p=NS$) were also similar between patients with and without IgG4-associated autoimmune hepatitis, respectively. One patient with classical AIH had anti-liver kidney microsome antibodies (type 2 autoimmune hepatitis).

Biological data were similar, except for gamma glutamyl transferase levels that were higher in IgG4-positive patients [31.4 vs 19.5 IU/l, $p=0.02$] (Table 2).

There were 3 overlap syndromes. Two patients had an overlap AIH + PBC (including one with an IgG4-associated autoimmune hepatitis). One patient had an overlap AIH + PSC (IgG4-associated autoimmune hepatitis). The MRI of this patient showed beading, band-like stricture and peripheral pruning more in favour of a “classical” PSC than an IgG4-related sclerosing cholangitis.

3) Comparison between patients with and without IgG4-associated autoimmune hepatitis during the follow up

The clinical and biological data were similar between the 2 groups (Table 2).

Two patients had a fulminant hepatitis. One (classical AIH) died at day 7 without the possibility of a liver transplantation, due to high age. Another (classical AIH) survived with a liver transplantation. Five patients were lost during follow-up: 1 patient with IgG4-associated AIH and 4 patients with classical AIH ($p=0.85$). There were no significant differences between patients lost during follow-up and other patients regarding age (67 [47.5-74] vs 49 [42-58.5] years, $p=0.14$), BMI (25.78 [21.5-28.8] vs 23.8 [21.8-25.8] kg/m^2 , $p=0.37$) and gender (W=3 vs W=16, $p=0.87$), respectively. Among the 5 patients lost during follow-up, one patient with IgG4-associated AIH and one patient with classical AIH were lost immediately after the hospitalization planned for the liver biopsy. No information on their treatment is available. The other three were lost during follow-up at one and two years of follow-up. Among the 28 patients

Table 2: Comparison of IgG4-associated AIH and classical AIH patients at baseline, at 12 and 24 months.

Variable	Data at baseline for IgG4-associated AIH	Data at baseline for classical AIH	Data at month 12 for IgG4-associated AIH	Data at month 12 for classical AIH	Data at month 24 for IgG4-associated AIH	Data at month 24 for classical AIH
BMI (kg/m²)	24.3 [22.5-30.6]	24.3 [21.7-25.9]	24.5 [23.1-29.5]	24.4 [21.9-25.6]	28.1 [19.8-34.4]	24.4 [22.2-17.2]
ASAT (IU/l)	236 [170-1298]	838 [269-1089]	25.5 [17.7-50]	30 [25-43]	24.5 [19.5-112]	35 [22.5-54.2]
ALAT (IU/l)	301 [151-1998]	776 [366-1565]	22.5 [21-73.2]	30 [20-39]	16 [15.2-91]	39.5 [25.5-66]
Gamma GT (IU/l)	248 [116-435]	153 [120-275]	48 [37.5-115]	47 [22.2-80.2]	35 [28-169.5]	40 [23.2-90.7]
alkaline phosphatase (IU/l)	184 [97-448]	176 [122-250]	64 [60.5-203]	72.5 [46.7-119.5]	102.5 [61.7-324]	64 [36-93.5]
Total Bilirubin (μmol/l)	20 [10-162]	37 [18-252]	8.5 [5.7-9.7]	14 [6-18.8]	7 [5-15]	11 [7-16.25]
Conjugated Bilirubin (μmol/l)	15 [3-139]	33 [7-163]	2 [2-4.25]	3 [2-5.5]	2 [0-5]	2 [2-5.5]
Gamma-globulin (g/l)	31.3* [24.1-43.7]	19.5* [13.6-28.3]	30.5 [30.5-30.5]	15.2 [12.0-16.9]	15.2 [15.2-15.2]	13.8 [12.8-20.4]
Total plasma IgG (g/l)	32.7 [18.1-40.8]	22.6 [17-32.3]	13.48 [9.7-24.7]	13.5 [11.9-18.9]	15.3 [7.1-27.4]	17.1 [12.7-20.8]
Dosage prednisone (g)	40 [40-60]	60 [40-60]	4.5 [0.8-12.5]	6 [4-10]	0 [0-2.2]	2 [0-6.2]
Dosage Aziathropine (mg)	50 [50-50]	50 [0-50]	50 [50-62.5]	50 [50-100]	50[50-87.5]	50 [0-100]

Quantitative variables are presented as the median and 25th-75th interquartile range.

* P=0.02 IgG4-associated AIH vs classical AIH.

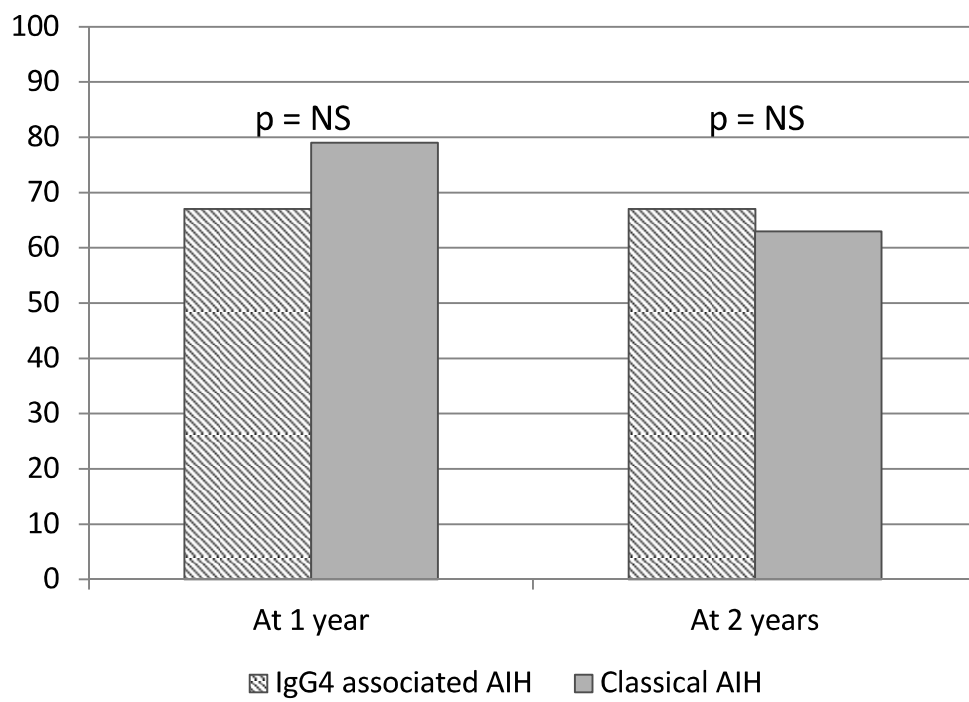
BMI = body mass index; ASAT = aspartyl aminotransferase; ALAT = alanine aminotransferase; gamma glutamyl transferase; IgG = immunoglobulin G

for whom the initial treatment is known, 27 received corticoids (including corticoids alone for 7 patients and the association of corticoids plus azathioprine for 20 patients). No difference on the initial treatment was present between patients with and without IgG4-associated AIH (6/6 patients IgG4-associated AIH versus 14/21 patients classical AIH receiving corticoid plus azathioprine, $p=0.41$). One 14-year-old patient with a classical AIH received cyclosporine alone. Amounts of corticoid were tapered regularly during the weeks following the start of the treatment.

After 2 years of follow-up, 2 out of 5 patients with IgG4-associated AIH and 12 out of 19 patients with classical AIH were under steroids ($p=0.35$). Two out of 5 patients with IgG4-associated AIH and 10 out of 19 patients with classical AIH were under steroids and azathioprine ($n=7$) or steroids and mycophenolate mofetil ($n=5$), $p=0.62$. Mycophenolate mofetil was introduced because of lack of efficacy or intolerance of azathioprin.

A complete biochemical response was defined by a normal level of ALT (≤ 35 UI/l for women and ≤ 50 UI/l for men). Four (67%) patients with IgG4-associated AIH and 15 (79%) patients with classical AIH had complete biochemical responses after 1 year ($p=0.54$). Two years following the diagnosis, 4 (67%) patients with IgG4-associated AIH and 12 (63%) patients with classical AIH had a complete biochemical response ($p=0.88$) (figure 4). Relapse was defined by an increased level of serum ALT at least 3-fold the upper limit of normal (>105 UI/l) under treatment. 1/6 (16.6%) patients with IgG4-associated AIH and 4/19 (21.1%) patients with classical AIH relapsed after 1 year ($p=0.81$). No patients with IgG4-associated AIH and 2/19 (10.5%) patients with classical AIH relapsed after 2 years ($p=0.41$).

Figure 4: percentage of complete biochemical response at 1 and 2 years



Discussion:

Here we report the first series of cases of IgG4-associated autoimmune hepatitis in European and North-African patients. These patients had similar clinical, biological and histological baseline characteristics, and followed similar disease evolution characteristics compared to patients with classical autoimmune hepatitis. Of note, complete biochemical responses were similar between IgG4-associated and classical AIH.

Except few case reports, only two studies among the literature have reported an IgG4-associated autoimmune hepatitis series of cases.

Umemura *et al.* is the first author to have introduced the term “IgG4-associated autoimmune hepatitis” in 2007 [13]. Presence of IgG4-associated autoimmune hepatitis was assessed in a study conducted in 60 Japanese patients diagnosed with type 1 AIH (82% of women, median age 58 years). IgG4-associated AIH was defined by “AIH according to the AIHG scoring system”: serum IgG4 concentration ≥ 135 mg/dL and immunostaining of IgG4 showing infiltration of ≥ 10 /High Power Field (HPF) IgG4-bearing plasma cells in the portal tract. Two patients (3%) met the criteria. Twenty-two patients showed cirrhosis among 31 bridging fibrosis. In the cohort, the 2 patients with IgG4-associated AIH had bridging fibrosis, higher median serum levels of IgG4, higher IgG4:IgG ratios, higher IgE levels compared with 58 patients with classical AIH. The 2 patients were treated with continuous low dose corticosteroid therapy (5-10mg/day) during the follow-up (5 and 13 years). All patients were treated with corticosteroids; none were given azathioprine [15].

Chung *et al.* published in 2011 a series of 26 Japanese patients (92% of women) diagnosed with a type 1 AIH [11]. The median age was 60 years old. IgG4-associated AIH was defined by “more than 5 IgG4+ plasma cells per HPF”. Positive staining for IgG4 was seen in 36.4% of patients (n=9). IgG4-associated AIH patients had significantly higher total serum IgG levels ($p < 0.01$). In contrast, there was no difference in serum IgG4 levels between the IgG4-associated AIH and the classical AIH. The degree of inflammation was more severe in IgG4-associated AIH patients. All patients were treated with prednisone according to an established protocol during the follow-up. None of the patients were treated with azathioprine, 6-mercaptopurine or cyclosporine. No difference was seen in the dose of prednisolone (initial and cumulative dose) between IgG4-associated and classical AIH patients. None of the patients with IgG4-associated AIH showed elevated levels of serum ALT on

prednisolone therapy. In contrast, 8 patients (50%) with classical AIH did show elevated levels of serum ALT, even on prednisolone therapy. No relapse was seen in the patients with IgG4-associated AIH. Six patients with classical AIH (37.5%) required incremental doses of prednisolone because of relapse. This led authors to suggest that IgG4-associated AIH could be associated with a better outcome than classical AIH.

In our cohort, there was no difference concerning the response to corticoids between IgG4-associated AIH and classical AIH. Although the modalities of treatment were similar between both groups, patients with IgG4-associated AIH and patients with classical AIH had a similar level of complete biochemical response at one and two years. Likewise, the level of relapse was similar between patients with IgG4-associated AIH and patients with classical AIH at one and two years.

These differences with Chung *et al.* could be explained by the fact that we introduced aziathropine for the majority of IgG4-associated (100%) and classical AIH (70%) patients. Moreover, the ethnic groups were different. Chung *et al.* and Umemura *et al.* studied Japanese patients, while we included mainly Caucasians (77 %) and North-African (23 %) patients. Finally, the number of patients enrolled in the three retrospective studies was relatively small, which could limit a definitive conclusion about the response under treatment between patients with and without IgG4-associated autoimmune hepatitis.

IgG4-associated AIH is a new entity. The question of whether the IgG4-associated AIH is a specific entity among AIH or a particular single organ manifestation of the IgG4-RD is still open. Similar questions can also be raised for other organ involvement. For example, specific renal involvement of the IgG4-related disease, named IgG4-related kidney disease, has been reported in Japanese studies [16–19]. The diagnostic criteria used were similar to those used by Umemura (≥ 10 plasma cells/HPF and an increase in IgG4 levels) [18,19]. All of 90% of the patients had a systemic IgG4-RD. The most commonly involved organs were the pancreas, the salivary glands and the lacrymal glands. The mean number of affected organs was 3.4. This entity seems to have a better response to corticoids compared to other renal diseases [16].

The physiopathology of the IgG4-related disease is still unclear. Genetic factors may be involved. The frequencies of human leukocyte antigen (HLA) serotypes DRB1-0405 and DQB1-0401 were significantly higher in Japanese patients

with type 1 autoimmune pancreatitis than in healthy individuals and in patients with chronic calcifying pancreatitis [20], whereas DQ β 1-57 without aspartic acid is associated with disease relapse in Korean populations [21]. The exact function of IgG4 in IgG4-RD is still not well understood. It is not known if IgG4 plays at an initial step in the occurrence of the disease. IgG4 production, like the production of IgE, may be controlled primarily by type 2 helper T (Th2) cells. Th2 cytokines such as interleukin (IL)-4 and IL-13 may enhance the production of both IgG4 and IgE. In contrast, IL-10, IL-12, and IL-21 may shift the balance between IgG4 and IgE, favouring IgG4 [22]. An investigation revealed that mRNA of forkhead box P3 (FOXP3), a regulatory T-specific transcriptional factor, in IgG4-related disease was expressed 36.4 folds higher than in classical autoimmune diseases [20]. Infiltration of FOXP3 regulatory T (Treg) in the liver of intra hepatic-IgG4 sclerosing cholangitis (SC) was significantly increased compared with primary sclerosing cholangitis patients. In addition, they found that the number of infiltrated FOXP3-positive cells was positively correlated with the number of IgG4-positive cells in intra-IgG4-SC patients [23]. The high concentration of FOXP3 was responsible for larges infiltrates of CD4+CD25+ Treg cells at affected sites and increased numbers of CD4+CD25+ high Treg cells in the blood. CD4+CD25+ Tregs produced IL-10, which may induce preferential switching of the B cell response in favour of producing IgG4 antibodies. In addition, tumor growth factor (TGF) β appears to be overexpressed in IgG4-RD [23,24]. Inflammation and subsequent fibrosis in IgG4-RD may be driven by Th2 cells and Treg cells. Conversely, autoimmune diseases are mediated by T helper 1 (Th1) or Th17 subset [25]. Increased Treg cells levels could correlate with the production of IL-10 in the involved organs.

Our study provides original data on IgG4-associated AIH. To our knowledge, it is the first study to assess a series of IgG4-associated autoimmune hepatitis in the Western world. We previously published a case report of a patient with a suspected IgG4 autoimmune hepatitis [26].

Moreover, one pathologist blinded to the clinical data reviewed all the liver biopsies. Our histological definition of IgG4-associated AIH was the same as Umemura's; thus allowing a high specific selection of patients. As a mono-centric study, a relative small number of patients were available and due to the retrospective collection of the data, we were not able to assess the IgG4 blood levels. However, elevated serum

IgG4 levels may help the diagnosis of IgG4-RD there are normal in up to 40% of patients with IgG4-RD [27].

In conclusion, we report for the first time that IgG4-associated autoimmune hepatitis may be seen in Western patients with AIH. Baseline clinical, biological and histological characteristics and the evolution of the disease seem to be similar to “classical AIH”. More prospective studies are necessary to check if IgG4-associated autoimmune hepatitis is a true entity or just a variant of classical AIH. A definition and a specific management of IgG4-associated AIH in Western patients could be then proposed.

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10-Feb-2015

IgG4-associated autoimmune hepatitis: an entity also present in Western countries

Dear Dr. Anty,

The editorial office of Liver International has received your recently submitted manuscript, entitled "IgG4-associated autoimmune hepatitis: an entity also present in Western countries" .

You will be informed of the decision as soon as possible. Your manuscript should not be submitted to another journal while under review at Liver International.

Please take note of the assigned number above for the purpose of all future correspondence pertaining to this manuscript.

Thank you for your interest in Liver International.

Yours Sincerely

Lynsey Rowland
Editorial Assistant Liver International



SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.