



**THE MEDICAL SOCIO-ECONOMIC BURDEN OF
AUTO-IMMUNE BLISTERING /BULLOUS DISEASES IN FRANCE
STUDY REALIZED BY THE PEMPHIGUS PEMPHIGOID ASSOCIATION OF FRANCE (APPF)
PRINCIPAL RESULTS : RESEARCH & POSSIBLE SOLUTIONS
SEPTEMBER 2015**

This study was conducted by the APPF, founded in 2005 by Josée de Felice, herself a pemphigus vulgaris patient, and, Isabelle Gentile, mother of child ill with a superficial pemphigus ; the two founders alternate as its president and vice-president. They founded the APPF to support patients afflicted with auto-immune bullous diseases and to facilitate exchanges between patients, their families and the medical community.

A list of acronyms and abbreviations can be found as an appendix at the end of this document.

Summary :

The information of this study relies on written and oral data collected by the Association. It comes from constant interaction over the past 10 years with patients subject to a dysfunctional immune system resulting in either a detachment of skin and/or mucuous cells or a detachment of the membrane linking the dermis to the epidermis. *

☐ Pemphigus vulgaris (PV), pemphigus foliaceus (PS), pemphigus paraneoplastic, bullous pemphigoid (PB), cicatricial pemphigoid (PC), pemphigoid gestationis, epidermolysis bullosa acquisita, linear IgA dermatosis, dermatitis herpetiformis.

The most frequently occurring auto-immune bullous diseases are treated with corticosteroids and immunosuppressants.

This study profiles the very cumulative burden made of a range of medical, pharmaceutical, social, legislative, administrative and economic difficulties.

This study highlights the diagnostic as well as the therapeutic trial and error obstacle course. Included as well are the intense limitations and disruptions to daily life which are shared by a lot of people suffering from rare chronic diseases.

This study mentions other significant characteristics :

- The policy of non-reimbursement for drugs as yet unlisted by the AMM (the French equivalent of the FDA) but which are necessary for the control of the disease may put patient's lives in danger
- Patients are insufficiently prepared to undertake clinical trials in which they have been encouraged to participate
- Given that a number of different organs are damaged, the need for pluridisciplinary, coordinated consultations is urgently necessary
- Patients are scared of sharing their anxieties with their doctors concerning therapeutic and medical prescriptions
- Closer and more open medical follow-ups of each patient's reactions would allow for better observance
- There are frequent demands for the recognition of alternative medicine as a complement to help better tolerate treatment
- Many patients feel strongly about the needs for psychological support of the concerning treatment and its secondary effects ; as of now, lacking financial support from state healthcare system, it is unavailable or non-existent
- There is much dissatisfaction concerning the difficulty in gaining access to knowledgeable teams of specialists and/or researchers

Rituximab, as has been shown in recent clinical trials on the drug's effectiveness in pemphigus, if given at the time of diagnosis or in the event of relapses, may very well eliminate many of the difficulties autoimmune bullous diseases patients encounter, reducing the chronic occurrence of relapse and the attendant costs.

The Two Parts of the Study (2012-2015)

In order to continue with its mission to serve the francophone population affected by auto-immune bullous diseases, the Pemphigus Pemphigoïde Association of France launched a qualitative study with the intention of getting an understanding of the different aspects of the medico-socio-economic « burden » borne by patients.

The first part of the study is a synthesis of 39 testimonies from auto-immune bullous disease patients' or their families' that have been published in the Association's bi-annual Newsletter.

The second part of the study is a synthesis of data gathered under strict confidentiality from :

- a) 3 years of telephone calls, emails or letters between patients or their families and the 2 founders of the Association acting as « listeners »
- b) a collective discussion between patients during the May 30 2015 General Assembly on topics that emerged from the above data for validation and research on solutions

This study could, among other possibilities, complete and give substance to statistical studies undertaken on the burden afflicting individuals done by larger organizations such as the RaDiCo FARD in the FIMARAD framework

The First Part of the Study : Collected from Testimonials Published in the « APPF Letter »

1. Sources

- This first part of the study draws on testimonials published in the 19 issues of the Association's Newsletter between November 2005 to November 2014. All these issues are accessible on the www.pemphigus.asso.fr site, and can be read in full in the section « your testimonials » on the APPF website.
- These testimonials whether spontaneous or solicited by the Newsletter come from patients and persons familiar with patients : wife/husband, child/parent. They are neither formatted nor the results of a preestablished questionnaire.
- Criteria for publication by the APPF are based on the correspondent's ability to remain objective, to manage his/her disease and to express a positive outlook of living with the disease.

- All accounts describe life after the onset of the disease. The patients convey incidents or circumstances which have struck them and what aspects they have suffered from the most.

2. Presentation of Results

- The 39 testimonials selected came from 24 women and 10 men. Some people expressed themselves several times, and their multiple accounts have allowed to follow the evolution of their disease and its effects on their lives over time.
- The « burden » described in these accounts is divided up by disease : 25 testimonials concern pemphigus and 14, pemphigoid.
- Whenever possible, the characteristics of the burden have been specified according to the stages of the disease : before diagnosis, during treatment, and after treatment.
- The testimonial summary charts (20 pages) are available at the APPF and can be sent by email on request to the Association : jacques.walch@free.fr

3. Description of the Burden from Published Testimonials

3.1 Common problems to all patients suffering from the same Auto-Immune Bullous Disease :

- **Diagnostic delay**, that is the time lapse between the first appearance of symptoms and clear, specific diagnosis, is a real problem – all testimonials express this.

This uncertainty is not only diagnostic, but also **therapeutic**. This part of the study reveals other causes in the delay of prescribing an adequate treatment : the unfamiliarity of dermatologists with the « PNDS » (National Protocols of Diagnosis and Treatment), and insufficient coordination between Referral Centers and personal and local sensitivities, cause avoidable delays and lead to discontent among patients. These delays are very difficult to live through as several testimonials report.

However, these testimonials are neither precise nor numerous enough to exactly measure the duration of each of these delays, diagnostic and therapeutic, during which the patient has to manage on his/her own.

Nor, according to these testimonials, is it possible to determine if, and in what way, the two National Plans on Rare Diseases (2005-2008, 2011-2016) have worked to the advantage of patients by reducing the delay time caused by these problems.

- After the anxiety and exhaustion of diagnostic delay is resolved, the **diagnosis** itself is the key moment around which the whole therapeutic configuration will take place. The end of uncertainty comes as a relief but also as a shock. The patient realizes that because the illness is chronic, he/she is in for a long course of treatment and that **his/her life is going to be different from now on.**
- Patients experience **significant pain** on the skin and on the mucous membranes. They experience difficulties in talking, eating, even breathing.
- **The physical alteration** due to symptoms and secondary effects of corticotherapy (swelling/puffiness of the face and neck, weight gain, hair growth, muscular loss) makes the disease visible, with an impact on the individual's social and professional lives. The patient has to accept the daily consequences of this, and bear the look of others on him.
- Patients accept the necessary no salt, no sugar and almost fat-free **diet** (PV & PS) with grim resignation ; it initiates new practices that can complicate daily life and reinforce isolation and stress – at the lunch room, during a business trip or a meal between friends.
- **Medical complications** like staphylococcus, loss of vision, heart problems, vitiligo, glaucoma, osteoporosis can make the health and social aspects of the patient's life more complex, as well influencing the way in which he/she will comply with the regimen of treatment : refusal to take cortisone, or, lowering the doses. Many begin to **examine non-conventional or alternative medicine.**
- The patient realizes quickly that he/she has to react and be **responsible for managing his/her disease.**
- Even if the crucial importance of **family support** is frequently mentioned, the exceptional nature of the disease makes communication difficult between the patient and his/her friends and family.

In their **work environment**, patients are even more reluctant to reveal their disease and do so only when there is no way to hide their ongoing suffering.

The vocabulary of **spirituality** is often used to evoke the experience of the disease ; but the private nature of such expression makes interpersonal communication even more challenging.

- In some cases, these testimonials express the relief brought by **hospital care** and by the **role of the APPF** in providing information, reassurance and direction. The Association works to prevent the patient's isolation and loss of courage by restoring hope.

3.2 Specific or punctual difficulties :

- The disease doesn't generally interfere with **pregnancy**, but the suitability of treatment as well as gynecological and dermatological care have to be followed closely. The future mother will have to make sure that the personnel of the maternity ward possesses the necessary skills for monitoring and treating her disease as part of the exceptional circumstances of her delivery.
- In order to avoid irrational attitudes from **kids at school**, a mother will have to make sure that her child's friends, teachers and school administrators are thoroughly informed about the nature of her child's disease.
- The continuation of **professional activity** is widely seen as a lifeline. Whatever the relational difficulties encountered at work may be, work is still preferable to stopping work altogether ; the social link is still maintained and the continuity of professional activity affirms the temporary nature of the disease.

However several testimonials indicate that depending on the stage of the disease's seriousness, patients must retain the option of going on sick-leave. Other testimonials point out the difficulty of convincing employers to adapt workplace conditions, materials used or workers'schedules to their disease.

4. Conclusion to This First Part of the Study Based on Testimonials

The burden imposed on patients ill with these auto-immune diseases is a human, medical and social reality. It involves familial and professional relationships. The burden is also an integral part of the disease, because when the difficulties patients are faced with are known, shared and taken into account, it can speed up remission

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The Second Part of the Study – Telephone Contact with Patients and Their Families

1. Listening : Source of the 2nd Part of This Study

Listening is a service covered by volunteers and provided by the APPF to people ill with auto-immune bullous diseases ; this service offers help and support in managing their disease.

Created in 2005, the Association provides information and follows up 200 members and approximately 500 non-members - patients or patients' family members who have given their names and contact details, desiring to receive documentation.

The training of volunteer « listeners » is conducted with the help of and in constant cooperation with the two auto-immune bullous disease Referral Centers and is reinforced by a training course.

The Association can currently rely on four « listeners ». Three other members of the APPF (two women and one man) are in training and will expand the team by the end of 2015. All the listeners are volunteers and have signed a confidentiality agreement binding them to the strict protection of patients' anonymity as required by the CNIL's regulations (Commission Nationale Informatique et Libertés – French and EU regulations)

1.1 Listening : the Organization of the Service :

Calls and mails are first received by Josée de Félice, and Isabelle Gentile, the two founders of the Association. These contacts are then dispatched to other trained listeners according to disease and location; a site specific network of listeners has been established in Normandy.

1.2 Types of Contact :

While the telephone is our widely used medium (60%) (from which, generic term of « listener »), other media are used as well, always at the initiation of the person in need : emails (30%), letters (9%), visits to the home of a « listener » (1%).

It would be useful to establish an office, a meeting point but the APPF has neither the means to rent a space nor the means to ensure it can be staffed. A lot of initial contacts by letter are followed up with telephone calls.

1.3 Number of Contacts :

Each of the 2 primary « listeners » receives an average of 20 calls a week, representing approximately a total of 40 calls a week. In May and August, the number of calls diminishes somewhat, but there are still always callers.

2. The Characteristics of Our Callers : 2012-2014

In order to be considered topical, this part of the study deals only with the last 3 years and draws only on elements stemming from the two primary « listeners », Josée de Felice and Isabelle Gentile

2.1 Geographical Origin of Callers :

Metropolitan France comes in first naturally. Then in decreasing order of frequency, calls come from French overseas departments, Belgium, Northern Africa except Tunisia, Francophone Africa, Eastern Europe and from various French expatriates in Asia and Canada.

2.2 Gender of Callers :

- 65% are female – either the patient, or a close family member/relative
- The remaining 35% are male : the patient's son, husband or the patient himself

2.3 Age and Disease of Callers :

- 50% of callers are over 50yrs old and are ill with pemphigus vulgaris, bullous pemphigoid, cicatricial pemphigoid

- 30% are between 30 and 50 and are affected with linear IgA dermatosis and epidermolysis bullosa acquisita
- 8% are young women ill with pemphigoid gestationis
- 2% of callers concern children or adolescents.
- 10% don't share their age because they are either familiar with a patient or because they are professionals who are only calling to ask general questions or find out technical information

2.4 Reasons for the Calls :

- 95% get in touch for problems relating to an auto-immune bullous disease
- 4% of the calls come from medical professionals (doctors, dentists, nurses) or retirement homes. Even if this percentage isn't very high, it is nonetheless important showing that professionals expect assistance from the APPF
- 1% of the calls concerns the patients' relations to the Association

2.5 Patients' Circumstances at First Contact :

- 20% of patients still have no diagnosis after having seen several doctors, dentists and stomatologists
- 30% are treated by local dermatologists
- 50% are treated in hospitals
- 4% of these are in Referral Centers

2.6 Motivation and Length of the Patient's First Call :

60% of callers call for the first time and the decision to contact the Association is largely motivated by :

- The need for information concerning the disease and its treatments
- Worry, fear or anxiety arising when faced with the disease's evolution and the side effects of treatments
- Exhaustion arising from the disease itself, its treatments, side effects and the hardships they cause in the patient's daily life

This first call can last up to 30 to 45 minutes because it takes time to listen, understand, explain, reassure, give advice, confidence and courage to the patient.

3. The Burden As Revealed in Patients' Needs and Questions

Some of the information provided by these calls completes and clarifies the profile of the burden's as already described in the first part of this study.

But, mainly, since the information is communicated in a state of urgency, as opposed to testimonies written calmly after the fact, it highlights new issues that can be classified in five groups.

Our « listening » starkly reveals the challenging question of the traditional boundary between the medical profession and grassroots patients' organizations as posed by the patients themselves

3.1 The First Group of Elements Is Striking Because of the Regularity with Which They Recur in Our Contacts with Patients :

These spoil the patients' daily lives and persist even after a diagnosis of remission. However, according to the patients, these elements are rarely taken into account by doctors who for the most part advise them to accept these problems with resignation being unavoidable. These elements are :

- Constant fatigue – this is mentionned by all patients whatever the autoimmune bullous disease may be ; the resulting discouragement makes it very difficult to complete any sort of project and thwarts the desire to do anything (sports, going out...). Yet, the response of many doctors is: « Everyone is tired »
- Digestive troubles such as vomiting, bloating, constipation/diarrhea, as well as headaches, and muscular and joint pain
- Loss of sleep
- Repeated infections (Ears-Nose-Throat, bronchitis, urinary infections)
- Loss of strength in arms and legs (PV) : « I feel I've aged 20 years »
- Itching day and night (PB) before the appearance of blisters, burning sensation on the skin (PV)
- Oral lesions (PV, PB, PC) which remain untreated because « they'll go away when the illness goes away » ; these are often followed by dental problems, tooth and gum discomfort that persit after remission (for example, after a tongue biopsy)

Minimalisation of these elements of the burden by the medical profession will lead some patients to look for alternative and/or non-conventional medicine in addition to their regular treatment: homeopathy, osteopathy, etiopathy, acupuncture, phytotherapy and sometimes even « spiritual » healers. The recourse to alternative therapies is rarely mentioned to the primary doctor « who doesn't want to understand and would be really angry with me », and often undertaken without assessing the risks involved and the possible consequences.

3.2 A Second Group of the Burden's Elements Shows the Significant Impact of the Disease on the Patient's Family And Social Relationships (this group concerns primarily patients suffering from pemphigus vulgaris) :

- Not recognizing oneself anymore : weight gain forcing the patient to change wardrobe ; body, face and neck deformity, scalp sores and hair loss which is difficult to conceal...
- Extreme difficulty in tolerating the relations of others to changes in appearance: difficult relationships with spouses, rejection and disgust from one's own children, isolation from friends, lies in order to protect oneself at work
- The strict no-salt diet with little sugar and no fat content exacerbates difficulties in family life, in the lunch room (at school and work), at restaurants (during business meals or meals with friends)
- Not knowing how to communicate anymore, not knowing whether or not to mention one's disease, and, when explaining it, having people turn away.

These elements cause the patient to isolate himself/herself, to keep quiet and withdraw within. Moreover, they will all too often cause him/her to cut back on his/her treatment or even to interrupt it all together without notifying the doctor, « in the hope of recovering a human face and figure »

3.3 A Third Group of Elements Points to a Lack of Medical Information And Support That Often Brings about Anxiety And, at Times, Rejection of Treatment by the Patient :

- What is perceived as excessive quantity of medicine and the need for constant special care over long periods of time

- The patient information leaflets in packages often cause alarm and, information found on the internet generates fear of « being poisoned » (corticosteroids) or of having « a cancer that is being hidden from me » (immuno-suppressors and rituximab). Following these last two points and as in 3.2, we notice, here too, that some patients decide to reduce or stop treatment altogether without informing their doctors for fear of not being treated anymore. « I didn't dare ask him/her what I would risk if I stopped the corticosteroids for 3 or 4 days so that I could have a break », « [I'd like to stop for]15 days to be able to go on a holiday »
- A pregnancy when the woman is ill with a bullous pemphigoid or a pemphigus vulgaris triggers a lot of questions on the part of the future mother about the consequences this might have on her baby – but, gynecologists and dermatologists pass each other the buck rather than accurately answering the patient's questions
- The possibility of relapse worries all patients ill with auto-immune bullous diseases because the alert signals have not been mentioned and therefore cannot be recognised by the patient and his family
- The risk or necessity of vaccinations is also poorly explained to patients under treatment with immuno-suppressors
- Clinical trials often proposed to patients are also problematic causing perplexity and uncertainty – particularly the contents of the consent for the text they have to sign : the notion of benefit and risk, the option to opt out of the trial (e.g, « I understood that if I decide to opt out of it, I will ruin everything for the others ; therefore, it's as if I can't opt out »), the notion of random selection which is discouraging, and, finally, the necessary opacity of the test's procedure as well as uncertainty as to how the patient will be informed of the end results

3.4 A Fourth Group Of Elements Concerns the Powerlessness Felt by Patients When Faced with What They Perceive As the Injustice, Hypocrisy Or Indifference of The Administration :

- Non-reimbursement of vital medicine : French law authorizes doctors to prescribe if necessary the medicine needed, but it will not be reimbursed by

state health insurance if it is being used « off-label » (AMM and CPAM issues). The majority of medications necessary to control our auto-immune bullous diseases are prescribed « off-label »; and, as most of these medications (corticosteroids and immuno-suppressors) are well known and have been on the market too long, their approval for other ailments than those for which they are habitually prescribed won't be profitable for pharmaceutical companies. Many patients never get refunded by the healthcare system and this could become the norm for all patients at any given moment. For the patient, feelings of incomprehension and anxiety compete with anger in the face of the injustice and incoherence of such policies. By comparison, most of pediatric medicine is prescribed « off-label » but is always reimbursed. The policy of non-reimbursement for auto-immune bullous diseases medicine is, therefore, a form of discrimination in the access to health care

- Dapsone is not available in France, despite the fact that this medication is significantly necessary because the authorized medicine, Disulone, raises ferritin levels. In order to get Dapsone, patients have to go through a hospital which has to put in a request for the medication (an administrative step called : ATU or temporary authorization of use); this lengthy and tedious process often results in a prohibitive augmentation of price by the laboratory concerned.

Therefore some patients have to buy their Dapsone on the internet or go to Belgium

- Refusal by some doctors to request for ALD special status in the National Health System for chronic diseases by which treatments are covered 100% : Doctors give three reasons for refusing to file a request :
 - « You won't get the ALD because your disease is not part of the 30 classified ALD traditional diseases ». This indicates a general ignorance of diseases covered by the ALD that are out of classification. In fact, the hospital that initially diagnosed the disease and prescribed the first treatment is indeed allowed to request for a 6 month ALD, after which the patient's GP can step in to renew the special coverage.

- « If you ask for an ALD, you will be identified by the National Health Services as having a rare disease for which the medicines haven't received approval – which means neither your medicine nor your medical care will be paid for by your health insurance (public or private) ». What can and should the patient do ? The situation is untenable. Nothing could be worse for the patient who's just discovered this administrative nightmare than to feel the anxiety of being singled out, becoming unable to continue his vital medical treatment without threat of financial ruin, censure or sanction (some of these monthly medicines are costly) ; he/she panics wondering « Are the health services going to ask me now to reimburse everything, including what has been paid for before ? » This fear was echoed by a pharmacist. « Am I going to be pursued for fraud ? »
- « Yes, perhaps we can request the ALD for all medical procedures relating to your bullous disease, but, certainly not for procedures relating to the side effects of your principal treatment ». This response on the part of GP's directly contradicts the position of the auto-immune bullous disease Referral centers and the PNDS (PNDS : French National Protocols for Diagnosis and Treatment) ; but, these two standards are generally unknown to doctors and local health service administrators, making it pointless to refer to them.
- Coverage of transportation costs to Referral Centers: There is a letter from the CNAMTS (health services for salaried workers) to the CPAM (general health services) stating that these costs have to be refunded ; but, here too, the local CPAM administration has the last word – some offices refund and some others don't.
- Difficulties consulting the the Referral Centers : The patient who is treated by a private doctor or at the hospital, and who after several months of inefficient treatment would like to have a second opinion (about his/her diagnosis and/or his/her treatment) will ask to join a Referral Center. But, when he/she asks his/her doctor to write the necessary letter of introduction to the Referral center, the doctor almost always refuses : « What does this specialist at the Referral Center know that I don't know? We had the

same training. Besides, he isn't obliged to see you ». The patient, then, contacts our Association hoping we can find a solution.

- Lack of multi-disciplinary medical consultations coordinated by one doctor: Auto-immune bullous diseases affect several organs (skin and mucous membrane) and the treatments' side effects impact on others (bones, eyes, heart, liver...). This results in patients having to schedule multiple appointments, not always easy to obtain within a time-frame necessary for correct treatment of the disease. Furthermore, in the confusion created by multiple consultations, patients don't always make the connections between their auto-immune bullous disease with symptoms present in various mucous membranes or symptoms triggered by their principal medical treatment. Also, when they see doctors other than dermatologists, they don't always think or are unable to explain their original illness.

In these last two instances due to lack of coordination, prescriptions and treatments overlap without consideration of possible negative interactions between them.

- Diagnostic and therapeutic delays occur frequently despite of the fact that the thorough efficient work of Referral Centers has decreased their frequency, and above all their duration. Incomprehension and anger are the frequent responses among patients experiencing the often needless proliferation and aggravation of the illness: e.g « Why don't they know how to say : I don't know and I will refer you to a colleague ? »

Our Association has all too frequently been witness to ignorance of the existence of the National Protocols for Diagnosis and Treatment as well as the Referral Centers

- Difference between pediatric services and adult medicine : In a pediatric service, the care of children and adolescents is often holistic and suited to each individual patient. The young patient feels secure and is taught the necessary habits. Adults, however, are on their own and current treatment practices oblige them to go from one service to another. They have to change their habits themselves, try to establish trusting relationships with new doctors, and perhaps even deal with different therapists' divergent assessments. It is often at this phase that failure to follow treatment begins.

- The Competence Centers' lists – established when the Referral Centers were first accredited, in 2004-2005 - are often outdated: the name of the person responsible for auto-immune bullous diseases is wrong or the specialist has left without being replaced.
- Difficulty, or even impossibility for PB and PV patients in some geographical areas to secure long-term, but essential nursing care. Doctors don't always think to provide health services with the right code (AMI 4) for this type of difficult, long-term care.
- Respect of patients' rights to privacy in regard to photographs. A number of callers have requested legal counsel after having been photographed without their permission by interns and medical students. Similarly, in some cases, teams of doctors will discuss a patient's illness in the patient's presence as if he/she weren't there. At times, these exchanges between doctors generate more anxiety in patients unprepared to hear what is being discussed.

3.5 A Fifth Group of Elements Contributing to the Burden of Our Diseases Concerns the Difficulty of Recovering from the Illness and Rebuilding a « Normal » Life outside the Medical Sector :

- Whether or not to « out » oneself in the workplace, to reveal or conceal one's illness : Consequences for social and professional life are potentially serious. A lot of patients, especially among younger ones, hide their disease in order to avoid professional complications.
- Problems in getting flexible working hours : A flexible working schedule allows one to get treated while maintaining one's job – which is essential since working is perceived by most patients as a lifesaver. Concrete knowledge of patients' rights and options in this area is nonexistent.
- At school, a child under corticosteroid treatment gets tired very easily, will have to miss classes and has to be on a strict no-salt regimen. Teachers and school administrators are poorly prepared to face up to these problems. Here again, information concerning rights and options is not available to families.
- Additional insurance premiums and loan refusals : some patients refuse to be registered as long-term patients (ALD) with the state health services for

fear of possible consequences affecting their insurance premiums and bank loan approvals they might need in the future. Both the consequences of and treatments for the disease have progressed, but insurance companies do not take these changes into account.

- How does one begin or resume athletic activity? While physical activity is a vital necessity, it requires strength that many patients no longer feel they possess. Adequate and supervision seem necessary to start or resume these activities.
- Possible risks of being under the sun, of sea bathing : precautions to be taken before a trip abroad. Patients request more specific information and advice in these areas.

4. Seeking Solutions to Reduce the Auto-Immune Bullous Disease Burden

4.1 Rituximab :

It is important to note that most of the elements of the burden listed above in 3 of the 5 groups would find an immediate solution if rituximab were to be administered to patients affected with an auto-immune bullous disease at the onset of diagnosis and at first sign of relapse. Based on the positive « risk/benefit » ratio results gathered from clinical randomized trials recently carried out on pemphigus vulgaris, administering rituximab early on would reduce the chronicity and cost of relapses as well as the after-effects persisting after remissions.

Intravenous infusions of rituximab allow the intake of corticosteroids to be reduced to a minimum and immunosuppressors often become unnecessary. Intravenous rituximab infusions would therefore eliminate the undesired side-effects of these drugs, as well as getting rid of anxieties which often lead patients to neglect follow-up care. As with all medicines, rituximab (chimeric monoclonal antibody) is not without undesired consequences, but the onset progressive multifocal leukoencephalopathy (PML) seems more than extremely rare in the framework of the treatment of auto-immune bullous diseases undertaken over the past 10 years. At any rate, once a physician has proposed rituximab treatment, it is up to the informed patient to decide whether or not to pursue this treatment based on his/her own assessment of risks vs. benefits.

4.2 Microbiota (intestinal flora) :

Recent research on gut microbiota and its interaction via the intestine with the nervous and immune systems, offers new prospects for alternative solutions to the health problems that complicate the daily life of patients with auto-immune bullous diseases (for instance, problems like fatigue, sleep, infections, pain...). The APPF will continue to establish contact with neurologists, neurological research, gastroenterologists, immunologists and micro-nutritionists. Two discussion sessions on this topic have already been held on February 13 and May 21 2016. As patients wait for the implementation of practical solutions resulting from this research, patients must carry on as best as they can. Other more traditional, one-time solutions lessen patients' hardship.

4.3 Response to the Need for Medical and Psychological Assistance and Follow-up Care :

- Creating a more open and frank relationship between patients and their dermatologists. How can this evolution in the doctor/patient relationship occur ? Patients on their side must be prepared for this development, but the problem is not one-sided. Might it be possible to implement a special training program to sensitize dermatologists? This could be undertaken under the auspices of the two Referral centers, the French Dermatology Society or the FIMARAD.
- Re-evaluating current treatment and care support in order to provide an improved observation and prevention of relapses. This improvement can be accomplished by :
 - a) A more complete oral explanation to be carried out by the doctor and/or nurse with the aid of supportive print media, ie. a leaflet or an information sheet
 - b) Close and regular medical monitoring of patients struggling with their treatment
 - c) Educational therapy for patients, doctors and paramedical practitioners

All these should be explored in concert with our 2 Referral centers and the Competence centers

- Responding to patients' need of psychological support in addressing underlying problems in their relationships working in concert with other associations concerned with the same issues, and in order to give substance to Professor Bodemer's proposal of a psychological assistance platform, we need to examine the patients' requests for psychological assistance from all angles (cf § 3.2), as well as how these requests can be met
- To look for the most appropriate location, as well as possible financing, for support groups comprised of patients who need them
- To expand existing patient therapeutic training programs or create new ones in conjunction with the Referral centers on recurrently troublesome issues, for instance : vaccinations, pregnancies, side effects of medications, clinical trials. A written and comprehensive document concerning these points will have to be produced and circulated to patients

4.4 Overcoming Administrative Difficulties:

- Non-reimbursement of medications prescribed off-label ; requests for a long-term 100% coverage from the National Health Services from GP's unfamiliar with our diseases ; the transition from « child/adolescent » to « adult » among patients initially diagnosed as minors - in all of these cases, we are confronted with either official documents or no documents at all preventing any decision making and allowing for policy inconsistencies and thus discrimination to become the norm.

These difficulties can only be solved by large administrative institutions to which a small association like ours has no access. Our only recourse is to exert continuous pressure, and, for this tactic to be efficient, it must rely on a comprehensive knowledge of our illness and its prior and current administrative status, of which policy-makers can be counted on as partners, as well as other recognized organizations. Once we can convince these potential allies, then, they will be able to support us !

Our first attempt at acquiring a regulatory text authorizing the reimbursement of necessary off-label medicines was delivered to the Ministry of Health by our Referral centers, by members of the National Assembly, the ANSM (agency that supervises medications' security), the

Rare Disease Foundation and the AFM-Telethon. No response was ever received.

For these reasons, we have to re-examine, along with other associations and in context of the FIMARAD's network, the ways in which we communicate our needs and difficulties (listed in § 3.4) to decision making bodies. Nonetheless, this shouldn't stop us from continuing to research and share what has already been accomplished – for instance, the study and examples of successful child/adult patient care processes featured in the AnDDi-Rares network.

- Circulating the PNDS and alerting doctors to the existence of the Referral centers. In order to reduce diagnostic delays and allow them to identify our auto-immune bullous diseases, doctors must be made aware of existing protocols and dedicated treatment centers. Since other FIMARAD associations have the same concern, this project could be studied with them and considered as a stepping stone to creating an inter-network with the objective of :
 - a) coordinating concerted actions from the Ministry of Health, from the French Order of Doctors, medical and scientific scholarly societies
 - b) creating publicity for medical journals, radio shows, etc.
- Gaining access to pluridisciplinary medical consultations or, at least, securing coordinated appointments as well as obtaining valorisation for long-term nursing care. These last two needs are shared with other FIMARAD associations, and as such, could lead to projects within the entire network.

4.5 Higher Insurance Premiums and Loan Rejections :

In addition to the purely medical aspects of the burden, as mentioned before, some patients refuse to be declared as long-term patients for fear of the consequences this might have on future insurance loans, in particular mortgage loans.

The right to privacy granted to ex-cancer patients which assures them normal insurance premiums, is enshrined in the Health law currently being debated in Parliament. One could hope that this disposition be extended to former patients afflicted with an auto-immune bullous disease.

However, this will be far from simple : can one ever be declared cured from an auto-immune bullous disease ? Would long-term remission be enough to trigger a right to privacy ? This debate is ahead of us.

As of now, some insurance companies are willing to curb their rates for our patients, but this is subject to their right to review statistics showing the typical trajectory of an illness. The APPF tried to provide such an overview but stumbled very quickly on the lack of reliable statistics (numbers per illness, age distribution, length of diagnostic delay, morbidity ratio, remission ratio, relapse ratio...)

The APPF wishes that the RaDiCo FARD database and the Rare Disease data bank might be made available, allowing for the establishment of a statistical norm to begin.

- As with the legal protection of patients seeking insurance and loan considerations, it is also necessary to establish a Therapeutic Patient Education (TPE) program adapted to specific needs of patients with auto-immune bullous diseases
- As is the case with many TPE programs, ours must be accompanied by detailed documents on procedures followed, as well as on the preparation of files and assistance provided for this preparation

4.6 Informing the Patients about their Rights :

Listening to patients has revealed the enormous lack of information patients receive about their rights and the opportunities at their disposal in the workplace, at school, in the hospital and at the MDPH (the house for people in situation of handicap)

A consideration of medical and associative aspects of rare diseases leads to the conclusion that the structural components of the burden (therapeutic education, statistical effort, psychological support, active management of patients' networks) are not the sole monopoly of Auto-Immune Bullous diseases ; they are found, to a greater or lesser degree, in many other rare diseases.

Networks grouping health partners, including patient associations, have arrived just at the right time to formulate the medico-socio-economic burden using a decompartmentalised approach and to identify what can be shared first in the FIMARAD's framework.

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Acronyms and abbreviations:

AMM (p. 1 & 11) : like the FDA (Food & drug Administration), this institution authorizes labels and marketing of medications

RaDiCoFARD (p. 2) : Study of rare diseases'burden on patients

FIMARAD (p. 2 & 17-18-19-20) : Network of dermatological rare diseases

PNDS (p. 4, 13 & 18) : National Protocols of Diagnosis & Treatments

CNIL (p. 6) : National Commission on Interactive Tecnology & Liberties

ENT (p. 9) : Ear-Nose & Throat

CPAM (p. 11 & 13) : State/National Health Services

ALD (p.12, 13 & 15) : Long-term illness – 100% health coverage for chronic illnesses

ATU (p. 12) : Temporary Authorization of Use (for some medicines like the Dapsone)

CNAMTS (p. 13) : Health Services for salaried Workers

ANSM (p. 18) (National Security Agency of Medicine)

AnDDI-Rares (p. 18) : Health Network Developmental Anomalies and Rare Causes of Cognitive Deficiency

TPE (p. 19) : Therapeutic Patient Education

MDPH (p. 20) : house/place for people in handicap