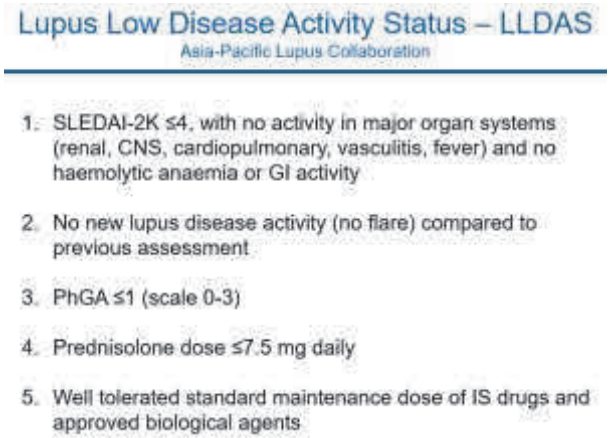
Annex 1 - Restoring hope

By Professor Frederic Houssiau, Rheumatologist at UCL St Luc Hospital.

While the fact that no new drug has been approved for lupus for so long can be interpreted as a lack of clinical progress, this is a very pessimistic look at the reality. The progress in lupus treatments has been and continues to be very encouraging, with falling mortality rates and a much better understanding of the disease that leads to substantially improved current care, and many reasons to hope further improvement is coming. Professor Houssiau highlighted five key areas in the clinical domain that are very solid reasons to hope:

1. Better defined target: In many diseases, targets for treatment are well defined. For example, in Hypertension, we know that if you reach the target of 130/80 mmHg, people will do well. In lupus, it is much more complex, and absent a target highly correlated with long term outcome, how to validate that a treatment plan really works? There has been huge progress in this area, with the development of LLDAS (Lupus Low Disease Activity Score), a Physician Global Assessment (PhGA) of disease activity, which correlates with long term outcome. Patients reaching LLDAS 50% of the time have 50% lower damage accrual after four years and report a significantly higher quality of life. In lupus nephritis, reaching a target of less than 0.7gr. proteinuria after 1 year brings a 94% probability of having a normal renal function after 10 years (missing it results in a 33% risk of renal failure), and thanks to the very long term follow up of patients in University Hospitals, we continue tracking this to establish the validity of this target to predict positive outcome after 20 or 30 years. Better defining targets is a huge improvement as it drives appropriate changes in treatment follow up.



2. Better use of old drugs: While we still use old drugs, we do it in a much better way than before. Survival rate of people with lupus nephritis, for example jumped from 50% at two years in 1950 to 90% at 10 years in 2010… so that is before biologics were approved for lupus nephritis. Hydroxychloroquine (HcQ), has for example long been used only for mild forms of lupus, because we did not know the action mechanisms, and hence thought it could be eliminated when "stronger" drugs were used. We now know it is a type 1 interferon regulator that should be used for all people with lupus. Its safety profile is very high, and it is the drug that is most correlated with survival rate in lupus. We also now understand how reduction of Glucocorticoids relates to damage accrual. This knowledge is driving treatment plans to move patients to 4mg max per day after one year, similar to what is done in Vasculitis. It does not work with everyone (75% success rate), but it should be tried with everyone.

3. The Euro-lupus regime has no gonad toxicity: In the Euro-lupus regime, treatment is induced with low-dose intravenous cyclophosphamide (6 x 500 mg IVCY q2w). The treatment works very well in most cases, and importantly, studies have now shown that this treatment regime has no gonad toxicity. This is a huge improvement for young women. Studies demonstrate that the anti-Müllerian hormone levels of women having received less than 3mg or between 3 and 6 mg of CYP are the same as those in the general population, so we now have an induction treatment for lupus nephritis that does not affect fertility.

4. Discovering effective multi-target therapies: the idea is that we should combine several drugs at induction. Instead of taking one drug or another, as was done historically, we are now looking at combining several drugs. An example is the combination of Voclosporin with MMF (Mycophenolate). Next to its calcineurin inhibitors blocking IL2 role, Voclosporin also stabilizes podocytes, which are cells that are protecting glomeruli, the key units of the kidneys. The phase II trial worked very well, comparing MMF + Voclosporin to

MMF + placebo, and implementing a fast reduction of Cortisone, patients with the combination therapy had twice more remission after a year.

5. Moving to targeted therapies and personalized medicine: Over the past years, plenty of trials, targeting plenty of different mechanisms of the lupus vicious circle have failed. The only successes have been the BLISS (Benlysta) ones. But several of those "failed trials" indicate positive results in some segments of the patients. Epratuzimab failed in phase three so did not get a label, but maybe worked. Rituximab (Mabthera) was repeatedly tested in lupus nephritis trials, always failing the primary endpoints. Yet, when lupologists used it for years with patients where everything else had failed, they obtained success in some 50% of patients! Today, many doctors use it "off label" in clinic, where it is legally allowed, because it works. It is not the first level drug, but possibly as much as 5% of people with active lupus around Europe receive it.

Target	Molecule	Trial acronym	L/LN	Phase	N	Results
B	Rituximab	EXPLORER	L	II/III	257	No benefit
		LUNAR	LN	III	144	11% more responders RTX but NS
	Ocrelizumab	BELONG	LN	III	381	Early terminated - Infections
	Epratuzumab	ALLEVIATE 1/2	L	II	90	Early terminated – Drug supply
		EMBLEM	L	IIb	227	More BICLA responders
		EMBODY 1/2	L	III	1574	No more BICLA responders
T	Abatacept		L	IIb	175	No less BILAG A/B flares
		ABATACEPT Trial	LN	II/III	298	No more renal remission
BAFF	Belimumab	BLISS 52	L	III	865	14% more SRI-4 responders
		BLISS 76	L	III	826	9% more SRI-4 responders
		BLISS SC	L	III	836	12% more SRI-4 responders
	Blisibimod	PEARL	L	III	547	No more SRI-5 resp w24
	Tabalumab	ILLUMINATE 1/2	L	III	2288	No more SRI-5 resp
	Atacicept (= >APRIL)	ATACICEPT Trial	LN	II/III	8	Early terminated - Infections
IFNa	Sifalimumab		L	II	431	14% more SRI-4 responders
	Anifrolumab	MUSE	L	II	305	17% more SRI-4/OCS taper responders
	Rontalizumab	ROSE	L	II	238	More SRI resp if ≥10 pred w0
	INF Kinoid		L	I/II	28	Down-regulation of IFN signature
IL6	Sirukumab	SIRUKIMAB Trial	LN	II	24	No more renal responders
Tweak	BIIB023	ATLAS	LN	II		Trial stopped interim analysis

The question of stem-cells is raised. Professor Houssiau answers that Hematic Stem-cells treatment worked in Systemic Sclerosis, but the problem is that you have 10% treatment related mortality… Placenta cordon stem-cells have different properties with regards to immunosuppression. And results have been surprisingly good, but the trials were not controlled, so it is difficult to use them as only base. Proper trials are in the pipeline, but with a low number of patients.

Recently, Anifrolumab was good in phase II, failed in one phase III… We are now awaiting the 2nd phase III that is still going on. The question must be raised of why so many trials fail. There might be an aspect of defining the right endpoints, due to the complexity and high variability of symptoms. Professor Houssiau makes the hypothesis that if we would have used LLDAS instead of other criterions, many trials would have worked. There is also the question of too much Glucocorticoids and immunosuppressant being given in the trials "base line", as it is very difficult to prove superiority when GC mask all short-term effects.

Precise medicine is what will make the difference in the next 10 years. No one drug will work for all, as is the case in rheumatoid arthritis. Today, we cannot anticipate who will respond to what drug, but the increasing availability of biomarkers will help better define what could work for patients. For example, 1/3rd of patients with lupus do not express type 1 IFN. It is then useless to give them drugs targeting type 1 IFN… isn't it? The idea of precise medicine is to identify signatures in a patient's blood (IFN signature, neutrophils, a type of B cells.) that correlates with that patient's lupus activity, and then target the treatment to the cells that create that signature…
Studies using Artificial Intelligence and big data are also in progress to identify, in kidney tissue, those gene expressions differentiating LN patients to classify them to understand and even predict who will do better in different treatment options. Technology is moving, knowledge is growing, and a lot is happening to bring better treatments to patients, allowing a positive look at the future.