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LECTURES

Neutrophils and immunity
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The main functions of neutrophils are thought to be limited to the initiation and amplification of the inflammatory response. However, such a reductionist view of neutrophils has been revolutionized by evidence supporting a relevant role of these cells in the modulation of both innate and adaptive immune responses. Accordingly, besides their classical bactericidal activities, neutrophils display an array of complex biological functions, including cytokine production, antigen presentation, release of neutrophil extracellular traps (NETs) and exosomes, expression/release of immunomodulatory molecules, whereby they can activate or downregulate innate and adaptive immune cells. Other data also support the view that distinct neutrophil subpopulations exist, particularly under pathological conditions. Hence, the awareness that neutrophils display phenotypical and functional heterogeneity is opening to novel fascinating discoveries on the potential immunoregulatory capacities of these cells. Furthermore, the discovery that neutrophils can populate the spleen and lymph nodes, under both homeostatic and inflammatory conditions, has strongly reinforced the concept that these cells, similarly to dendritic cells (DCs) and macrophages, can deliver signals that drive not only innate but also adaptive immune responses. During my talk, I will give a brief overview on the most recent and significant studies on the involvement of neutrophils in immunity.

Neutrophilic dermatoses : History of ideas
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In the history of our conception of the neutrophilic dermatoses, three periods can be identified:
1 – Description of specific skin conditions
This period started in 1908 with Brocq and Simon's description of "geometric phagedenism", which was better defined as pyoderma gangrenosum (PG) by Brunsting et al. in 1930. The second important description is due to Sweet, who described in 1964 the syndrome named after him (SS).
2 – Individualization of a Neutrophilic Dermatoses spectrum.
The report of patients with overlapping conditions led to the discovery of a tight link between PG and SS. Other clinical entities, such as Sneddon-Wilkinson's disease, erythema elevatum diutinum, and others, could also be considered as belonging to a unique spectrum of neutrophilic dermatoses, with clear criteria (Wallach, 1991) including the frequent association with multisystemic disorders. The occurrence of neutrophilic infiltrates in internal organs was named the neutrophilic disease. A simple clinical-pathological classification of the ND was proposed in 2006 (Wallach and Vignon-Pennamen).
3 – Discovery that the Neutrophilic Dermatoses are cutaneous expressions of auto-inflammation.
Starting in 1997 with the description of the PAPA syndrome (Lindor et al.) it could be hypothesized that auto-inflammation, the inappropriate activation of innate immunity, induces both monogenic auto-inflammatory diseases and the complex cutaneous conditions known as the neutrophilic dermatoses.

Cardiometabolic comorbidities of psoriasis: where we stand

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From the well-known article published by Gelfand et al in 2006, psoriasis was epidemiologically identified as a risk factor to an increase in cardiovascular comorbidities, particularly in young patients with the most severe forms of the disease. From this point on, despite some controversies, a clear majority of studies using different methodological approaches have suggested not only an association of psoriasis with cardiovascular diseases but also have provided the evidence for psoriasis as an independent cardiovascular risk factor. However, causes and consequences of this association are controversial.

Although some genetic overlap between psoriasis and several of its comorbid conditions exists, the observed association of psoriasis with cardiovascular comorbidity cannot satisfyingly be explained by shared genetics. On the contrary, it may be partly explained by common shared inflammatory pathways. Atherosclerosis, which was formerly viewed as a cholesterol storage disease leading to flow-limiting stenosis, is now defined as a chronic immune-mediated inflammatory disease. Chronic skin inflammation may lead to vascular and systemic inflammation, atherosclerosis, and thrombosis. The pathogenetic link between psoriasis and cardiovascular comorbidity is likely provided through insulin resistance and endothelial dysfunction, as these are known drivers for atherosclerosis. Both adaptative and innate immune system have been proposed to play a role in atherosclerosis and psoriasis.

Th1 cells are also critical to the process of atherosclerosis, thought to be primarily driven by IFN-γ, the hallmark cytokine of the Th1 response. it has been suggested that the IL-17A/neutrophil axis could also take part to atherogenesis associated with psoriatic disease. Nevertheless, the role of IL-17A in psoriasis-associated anti- and pro-atherogenic effects, depending on the inflammatory context. Neutrophil-macrophage communication is involved in the inflammation that aggravates atherosclerosis, and particularly NETosis seems to play an important role.

Therapeutic strategies could have an impact not only in the skin lesions but also eventually in the CV comorbidities. Observational studies involving numerous registries have reported reduction in myocardial infarction in patients treated with tumor necrosis factor antagonists. A recent study showed that ustekinumab may improve coronary and myocardial function in psoriasis patients. The effects of various biologic anti-inflammatory therapies including adalimumab, ustekinumab and secukinumab are being evaluated in moderate- to-severe psoriasis.

Vasculitis syndromes

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All vasculitic syndromes show as least common denominator the basic reaction pattern of leukocytoklastic vasculitis, namely accentuation of neutrophils and nuclear dust around postcapillary venules. Besides an algorithmic approach which gives a better understanding for pathogenesis main focus will be on medium vessel vasculitides as well as their clinicopathological correlations.

Granulomatosis with polyangiitis, previously Wegener granulomatosis (GPA), is a classical small and large vessel disease characterized by frequent involvement of ear-nose-throat-eye, lungs and kidneys plus the presence of cytoplasmic anti-neutrophilic cytoplasmic antibodies (c-ANCA; antigen is proteinase 3). Skin involvement occurs in 30% of patients usually in due course of disease. Yet, there are monosymptomatic variants of eye, ENT or other organs which may persist for years, and c-ANCA may be negative. GPA affects all ages and races and occurs without sexual predilection. In Dermatology the head, upper extremity and trunk (in particular the buttock) are besides the mucous membranes of mouth, nose, ear and eye the most often involved locations easily to access for diagnostic biopsy. Patients present with oedematous to haemorrhagic and/or necrotic plaques, nodules, tumours or ulcers. In the lungs massive haemorrhage is characteristic, while the kidneys show early glomerulonephritis which causes haematuria, proteinuria and in due course a decrease in glomerular filtration rate.

Eosinophilic granulomatosis with polyangiitis, previously Churg-Strauss-syndrome (EGPA), is a classical small and large vessel disease histologically similar to GPA, but with prominence of eosinophils. Patients frequently suffer from preexisting and/or concomitant atopic dermatitis, pollinosis, and/or asthma. c-ANCA are negative, yet there is variable perinuclear-ANCA (p-ANCA; antigen is myeloperoxidase) expression. EGPA is a rare disease and was previously more common (probably due to reduction of use of sulfonamides?). Internal organ involvement usually is mild. Gut, lung, heart, kidney, central and peripheral nerve system may be affected. Macules, patches, papules and plaques of small vessel vasculitis are most commonly seen on the trunk, nodules and tumours of large vessel vasculitis on the head, upper extremities or trunk. There may be an early haemorrhagic character; late brownish pigmentation similar to urticarial vasculitis may mimic morphea or early mycosis fungoides.

Microscopic polyangiitis (MPA) is a classical small and large vessel disease histologically similar to GPA and EGPA, but without granuloma formation. MPA is a rare disease, in particular in skin. Internal organ involvement usually is more prominent. Gut (bowel infarcts), lung (hemorrhage, hemoptysis, infiltrates), heart (heart attack), kidney (hematuria, nephritis, kidney failure), central (stroke) and peripheral nerve system may be affected. Adults, males and females, characteristically present with erythema nodosum-like changes, yet palpable purpura and/or livedo patterning may occur. Serologically, one frequently finds perinuclear-ANCA (p-ANCA; antigen is myeloperoxidase) expression. There may be an early haemorrhagic character.
Cutaneous polyarteritis nodosa (CPN) is a classical medium vessel disease usually without small vessel involvement and no granuloma formation. Adults, male and female, early suffer from ancle pain/arthritis and develop livedo patterning with – when classic - nodules in moniliforme presentation. In the vast majority internal or other organs than skin are not involved with the exception of peripheral nerves and/or close-by striated muscles. CPN usually is ANCA negative. I do not have experience with cases of systemic polyarteritis nodosa which simultaneously or subsequently involved skin or subcutis.
Histology of GPA, EGPA and MPA show as a basic reaction pattern a leukocytoclastic vasculitis of small and large vessels; GPA characteristically shows collagen degeneration to necroses with large basophilic geographical necroses surrounded by palisading macrophages (granulomas), EGPA a similar profile with prominent eosinophils and thus eosinophilic necroses, small as flame figures, large as geograpical necroses. MPA is without granulomas. In contrast to these small and medium vessel disorders CPN affects medium vessels only without significant surrounding tissue damage or granulomas.

Hidradenitis suppurativa

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Hidradenitis suppurativa/acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease, which presents after puberty with painful, inflamed lesions in apocrine gland-bearing areas of the body. It leads to significantly impaired quality of life, depression and working disability and exhibits co-morbidities like spondyloarthropathy, inflammatory bowel disease, smoking, obesity and metabolic syndrome, which increase the disease burden and substantially affect patient health-related quality of life outcomes (HRQoL). The cause of HS is multifactorial. The nature of the disease, its comorbidities and its pathogenetic pathways appears to be at large extent similar with psoriasis. Treatment of HS varies widely and includes medical treatments like local or systemic antibiotics, hormones, retinoids, systemic immunosuppressive and anti-inflammatory agents and surgical options like deroofing, wide excision and CO2 laser. However, most treatments are supported by low quality of evidence and outcomes used in these studies are not validated nor represent clinical important outcomes. Adalimumab is the only officially approved treatment option for HS. The need for high quality evidence on combination of treatments, treat to target and long term management is urgent. Advances in understanding the pathogenetic pathways of HS led to new anti-inflammatory and immunoregulatory drugs currently in the pipeline which appear promising.

Immune regulation in skin disease: IL-17 and the TReg/Teffector balance

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Currently paradigm shifts are taking place in immune-mediated human skin disorders. Nowadays, as in many other auto-immune diseases, focus is on imbalances in the regulatory T cell (Treg)-Th17over the formely suspected Th1/Th2 ratio. Also, besides T cells, innate immune cells come into play as co-expressors of IL-17. However, our understanding of this pathways is still limited and much needs to be clarified. We showed that Treg of patients with severe psoriasis easily differentiate intoIL-17A-producing cells and that these patients reveal 17A+/Foxp3+/CD4+ positive cells in lesional skin. In a humanized mouse model of skin inflammation we confirmed influx of IL-17A producing human CD4+ and CD8+ T cells, as well as immunoregulatory CD4+Foxp3+cells. This was supported using a human margin zone model, where the relatively high Foxp3/CD4 ratio in symptomless skin of patients with psoriasis suggests an activate immune controlling mechanism distant from the psoriatic plaque. In the margin and centre of the plaque the ratio was skewed towards effectors cells associated with inflammation. To our surprise, IL17, an important driver of the psoriatic process, appeared mostly related to innate cells, and far less to T cells. Then, we characterized IL 17 expressing immune cells over time, using two established in vivo dynamic models of human skin inflammation that share many histological features with psoriasis, i.e., leukotriene B4 application and tape-stripping. Immune histochemical staining for IL-17 revealed that the majority of infiltrating cells that stained for IL-17 were neutrophils and mast cells, in both models; IL-17 producing T cells were less abundant. Thus, blocking IL-17 with targeted treatments might be more far-reaching

thanpreviously thought; not only IL-17 production by T cells, but also innate immune cell function may be blocked. Furthermore, therapies specifically targeting IL-17 may not only improve psoriasis, but also prevent comorbidity that is associated with the IL-17 pathway, hereby preventing serious complication on the long run.

12th October 2018

Alopecia areata

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Alopecia areata (AA) is a chronic relapsing, T-cell mediated autoimmune disorder characterized by non-scarring hair loss affecting children and adults across all ages, races and sexes (1-2). AA is associated with other immune diseases including asthma, allergic rhinitis, atopic dermatitis, and autoimmune diseases such as thyroiditis and vitiligo (2).
Cells involved in the pathogenesis include CD8+ T cells, NK cells, and mast cells. The possible inflammatory pathways include cytokines from the TH1 axis, including IFN, IFN, and IP-10. Mouse models have shown that IL-2 ad IL-15 play a role in the initiation of autoreactive CD8+ cells that attack hair follicles (3).
Clinical presentation of AA can be limited to small, circular patches of scalp hair loss (Patchy hair loss), involve complete loss of hair on the scalp (alopecia universalis, AT), or total loss on the scalp and body (alopecia universalis, AU). AA involving 50% or greater scalp hair loss, including AT and AU, is considered and advanced form of alopecia, with poor prognosis for hair regrowth.

1) Gilhar A. Collapse of immune privilege in alopecia areata: coincidental or substantial? J Invest Dermatol. 2010; 130:2535-7.
2) Hordinsky MK. Overview of alopecia areata. J Investig Dermatol Symp Proc. 2013; 16: S13-5.
3) Suárez-Fariñas et al. Alopecia areata profiling shows TH1, TH2, and IL-23 cytokine activation without parallel TH17/TH22 skewing. J Allergy Clin Immunol. 2015; 136: 1277-87.

What's new in the systemic treatment of psoriasis: dimethyl fumarate

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Fumaric acid esters (FAEs) have been the most commonly used drug for moderate-to-severe psoriasis in Germany for many years and are now available to physicians all over Europe.
The conventional FAE product used in Germany since 1994 is a mixture of several FAEs. The biological active substance for psoriasis is Dimethylfumarate (DMF). The novel EMA approved drug contains only DMF. The onset of action of FAEs for psoriasis is relatively slow. FAEs are not like a sprinter but much more like a marathon runner. FAEs are uptitrated for several weeks, starting from 30 mg up to 720 mg daily dose, though in most patients a maximum dose of 360 – 480 mg is sufficient. Efficacy should be assessed around week 24, though further improvements beyond week 24 are not rare. After a stable clinical efficacy is achieved, the daily dose may be decreased stepwise until the minimal maintenance dose is reached. FAEs have common and substance specific side effects. Usually, patients experience side effects long before they notice their skin improving. Hence, careful and detailed explanation of the expected time points for side effects and onset of action of FAEs are key for good adherence of patients to the medication. To help patients during the first months of FAE treatment, topical therapy and/or UV-therapy can be combined to achieve a faster onset of action.
FAEs can provide good long-term control of the disease and dose adaptations are possible to react to an individual's disease activity at any time. To optimise treatment outcome and patient adherence, certain drug specific aspects have become familiar to physicians and patients; FAEs may cause gastrointestinal (GI) symptoms and flushing, especially during the uptitration period. GI problems can be minimised in many cases by individualised dosing, i.e. increasing the dose only in very small steps or temporarily decreasing the dose until the symptoms become highly tolerable.
Safety monitoring includes regular blood and urine tests. Most important values include leucocyte and lymphocyte counts and kidney function parameters. If values are fine, tests every three months are enough during long-term therapy with DMF.
In this presentation, clinical study data and recommendations on how to use FAEs in daily practice will be provided.

Ixekizumab
L. Puig

This presentation will review the available evidence and real life clinical data on the use of ixekizumab in the treatment of psoriasis. Ixekizumab is a humanized immunoglobulin (Ig) G subclass 4 (IgG4) monoclonal antibody that selectively binds with high affinity (Kd< 3 pM at 37ºC) to human IL-17A, a key mediator in the pathogenesis of psoriasis. Ixekizumab has proven to be one of the most efficacious therapies for moderate to severe psoriasis; with ixekizumab 80 mg every 2 weeks, the frequency of patients achieving PASI 75/90/100 at Week 12 was nearly 90%/70%/40%. Head-to-head trials have shown superiority of ixekizumab to etanercept and ustekinumab. The efficacy of ixekizumab has been shown to persist with maintenance treatment every 4 weeks; the mean PASI was 1.4 and 80% of patients remained on absolute PASI values equal to or lower than 2 after 3-years of treatment (multiple imputation analysis of missing data). Ixekizumab has been shown to be effective in the treatment of other types of psoriasis, including palmoplantar, erythrodermic, generalized pustular and nail psoriasis. It has also been shown to be effective for treatment of psoriatic arthritis in a phase III study. Ixekizumab is well tolerated by patients, with the most common adverse events being injection site reactions and infections such as nasopharyngitis, and upper respiratory tract infections.

Pustular psoriasis
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Pustular psoriasis subtypes are mainly consisting of localized,including palmo-plantar pustulosis (PPP),and acrodermatitiscontinua ofHallopeau,and generalized or disseminated forms.These last years identification in patients with generalised pustular psoriasis (GPP) or with PPP and ACH of homozygous or composite heterozygous mutations targeting the interleukin-36pathway, provided the first evidence for a monogenic model in pustular psoriasis. Further studies also lead to the detection of mutations of the same gene in a subset of patients with drug-induced acute exanthematous generalised pustular eruption (AGEP). These findings led to the specific design of drugs aiming to inhibit the IL-36 inflammatory pathway, with ongoing studies in GPP and PPP.These studies are likely to challenge the current treatment algorythms in PPP and in GPP,with little evidence for the efficacy of conventional or biological drugs.

Bullous pemphigoid: from the bench to the clinic
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Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease of the skin. It is associated with autoantibodies directed against the BP antigen 180 (BP180, BPAG2) and the BP antigen 230 (BP230 or BPAG1), components of junctional adhesion complexes called hemidesmosomes. It is usually a chronic disease affecting the elderly with spontaneous exacerbations, which may be accompanied by significant morbidity and mortality. The spectrum of clinical presentations is extremely broad. Although widespread blister formation often occurs, in up to 20% of the patients only excoriated, eczematous or urticarial lesions (either localized or generalized) are present. The diagnosis, which may represent a real challenge, relies on the detection of linear deposits of IgG and or C3 along the epidermal basement membrane zone. Potent topical corticosteroids represent the first therapeutic option in BP wherever feasible, although systemic steroids are also effective . The latter are however associated with an increased number of side effects and mortality. There is little convincing evidence supporting the systematic use of other therapies, such as immunosuppressive drugs or antibiotics. Rituximab and omalizumab have been used with some success in small case series. New targeted therapies are currently being developed.

Skin manifestations of the autoinflammatory syndromes
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Pyoderma gangrenosum is a rare inflammatory neutrophilic dermatosis manifesting as painful ulcers with violaceous, undermined borders on the lower extremities. It may occur in the context of classic syndromes like PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) and SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis), as well as in a recently described entity named PASH (pyoderma gangrenosum, acne and suppurative hidradenitis). Pyoderma gangrenosum has recently been included within the spectrum of autoinflammatory diseases, which are characterized

by recurrent episodes of sterile inflammation, without circulating autoantibodies and autoreactive T cells. In PAPA syndrome, different mutations involving the PSTPIP1 gene, via an increased binding affinity to pyrin, induce the assembly of inflammasomes. These are molecular platforms involved in the activation of caspase 1, a protease that cleaves inactive prointerleukin (pro-IL)-1β to its active isoform IL-1β. The overproduction of IL-1β triggers the release of a number of proinflammatory cytokines and chemokines, which are responsible for the recruitment and activation of neutrophils, leading to neutrophil-mediated inflammation. In SAPHO syndrome, the activation of the PSTPIP2 inflammasome has been suggested to play a role in inducing the dysfunction of the innate immune system. Patients with PASH have recently been reported to present alterations of genes involved in well-known autoinflammatory diseases, such as PSTPIP1, MEFV, NOD2 and NLRP3. Pyoderma gangrenosum and its syndromic forms can be regarded as a single clinicopathological spectrum in the context of autoinflammation.

Role of dermatologists in the management of psoriatic arthritis

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Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis (PsO). Both disorders share common pathogenic mechanisms involving genetic and environmental factors. Because PsO is typically present for years before symptoms of PsA emerge, dermatologists are in a privileged position to detect PsA early through regular screening of patients. The most useful screening questionnaires include the Psoriatic Arthritis Screening Evaluation (PASE), the Psoriasis Epidemiological Screening Trial (PEST), the Early ARthritis Psoriatic questionnaire (EARP) and the Psoriatic Arthritis Screening (SiPAS) questionnaire. It has been repeatedly reported that PsA is under-diagnosed in PsO patients, which may be due to under-recognition of musculoskeletal symptoms by dermatologists. Dermatologists are not well trained to distinguish muscle-skeletal inflammatory symptoms including pain, related to inflammatory disorders such as PsA, from non-inflammatory symptoms, related to other muscle-skeletal disorders, such as osteoarthritis. Moreover, an average of 5 years delay elapses between signs/symptoms onset and PsA diagnosis. Early diagnosis and prompt therapeutic intervention are crucial for limiting PsA progression, prevention of disability and improvement of quality of life. Joint damage may develop in the first years of the PsA course, and even a 6-month diagnostic delay contributes to worse long-term radiographic and functional outcomes. Therefore, dermatologists play a crucial role in the early identification of patients with PsA and in preventing irreversible joint damage. Finally, the creation of multidisciplinary clinical settings with dermatologists and rheumatologists working together may significantly increase PsA detection and improve the management of PsA.

Chronic Urticaria

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Chronic urticaria is a common disease that is characterized by the recurrent appearance of itchy wheals, angioedema, or both, either in response to a specific stimulus (in chronic inducible urticaria, CINDU) or occurring spontaneously (in chronic spontaneous urticaria, CSU). In chronic urticaria, quality of life is often dramatically impaired in those patients who are not optimally managed and who do not receive effective therapy. To provide an optimal management of our patients with urticaria, we should understand the most important aspects of the pathophysiology, be aware of potential differential diagnoses, and know the current treatment guidelines.
An effective treatment for urticaria patients should always aim for complete control of symptoms. This can only be achieved if we fully assess the symptoms and the burden of our patients, rule out differential diagnoses such as autoinflammatory syndromes, urticaria vasculitis or bradykinin mediated angioedema, and finally follow the current treatment guidelines. The standard treatment in any urticaria patient is and will be antihistamines in standard or, if required, higher doses. This is based on our knowledge that signs and symptoms of urticaria are brought about by histamine released from mast cells. However, many patients still suffer from urticaria despite proper antihistamine treatment. In these patients, the currently only licensed drug is Omalizumab, an anti-IgE treatment. Up to 70 % of our patients can be sufficiently controlled using this treatment, many responding within a few days. There is new evidence that these early responders to Omalizumab are patients with type I autoallergy, i.e. these patients have IgE that is directed against self-proteins. The other group of patients responding after 1 to 3 months to Omalizumab are considered to be type IIb autoimmune patients where IgG autoantibodies are directed for example against the IgE receptor.
Regardless of the underlying pathophysiology in our urticaria patients, a correct diagnosis and a proper treatment will enable us to effectively treat the majority of our patients. New treatment alternatives currently in early phases of

clinical trials will hopefully be able to treat the remaining patients who are not sufficiently treated by antihistamines or Omalizumab.

Pharmacogenomics of psoriasis: where we stand

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Psoriasis is a chronic, multifactorial disease resulting from complex interactions between genetics, immune system, and environmental factors. The heterogeneity of response to treatment of psoriatic patients is widely recognized in terms both of efficacy and toxicity. The availability of predictive response biomarkers could enable achieving higher response rates faster, at the same time reducing adverse events and healthcare costs. Pharmacogenomics is the study of inter-individual variations in DNA sequence that are related to drug response. Single nucleotide polymorphism (SNPs), mainly involved in pharmacokinetics, have been linked with response to conventional anti-psoriatic drugs. In addition, genetic variations in some of the psoriasis susceptibility genes associated with innate and adaptive immunity have been correlated also to response to biologics. To date, clinical implementation of pharmacogenomics into therapeutic algorithms has been limited also by low reproducibility of currently available data. In the perspective of newer, more effective drugs for psoriasis, it is likely that genotype could be integrated with phenotypic markers to more specifically characterize each individual patient.

13th October 2018

Atopic dermatitis: advances in treatment

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The pathogenesis of atopic dermatitis is multifactorial, and the clinical presentation of the condition varies greatly. Symptoms and severity of disease are heavily dependent on individual factors and stage of the disease. The majority of atopic dermatitis patients experience a sufficient clinical response to emollients in combination with one or several of existing topical or systemic therapies, but treatment failure with existing drugs and treatment options can represent a significant clinical problem. Therefore, it is encouraging that some new treatments are already registered for clinical use, and some are in the pipeline, and the bulk of these anti-inflammatory drugs focus on reverting a skewed immune response in atopic dermatitis. Novel therapeutic approaches which target the pathways involved in the pathogenesis of the disease provide the opportunity for a potentially more effective and less harmful approach to both topical and systemic therapy. These pharmaceutical agents are often designed to narrowly modify or directly block a specific signal or pro-inflammatory pathway. Novel approaches to proactive treatment have also been developed. New insight in these treatment options will be provided.

FREE COMMUNICATIONS

T cell subsets shape the clinical phenotype in autoimmunity against desmosomal and hemidesmosomal adhesion molecules

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There is a plethora of evidence provided by our group and others that pemphigus and bullous pemphigoid (BP) are linked to a T helper 2 (Th2) response against desmogleins (Dsg) 1/3 and BP180/BP230, respectively. We here show that T cell recognition of these autoantigens is not restricted to autoimmune bullous skin disorders but also seen in the chronic inflammatory skin disorder, lichen planus (LP), although with an opposing cytokine profile. Immunologically, LP is characterized by a profound mixed dermal CD8+ and CD4+ T cell infiltrate with an IFN-□-dominated signature. Although T lymphocytes are assumed to play a major role in disease development, the targeted skin antigens are largely unknown. By EliSPOT analysis of peripheral blood T cells from a cohort of 52 patients with muco-cutaneous LP, we identified autoreactive Th1 and Th17 responses against the NC16a domain of BP180 and Th1 cell responses against the Dsg3 ectodomain. Moreover, LP skin lesions showed a T-bet (Th1)-dominated dermal infiltrate while skin lesions of BP and pemphigus patients showed a GATA-3 (Th2)-dominated inflammatory infiltrate. These findings were associated with the accumulation of Th17 cells at the BMZ of LP skin lesions whereas Th17 cells were scattered in the upper dermis of BP and pemphigus skin lesions. Of note, three patients with LP pemphigoides (LPP), a rare clinical sequela of LP, showed a mixed peripheral blood Th1/Th2 cellular response against BP180-NC16a and a mixed Th1/Th2 cell infiltrate of lesional skin which led us to conclude that LPP is a clinical and immunological

chimera of LP (Th1 driven) and BP (Th2-dominated). Finally, treatment with secukinumab, a monoclonal antibody against IL-17a, of three patients with recalcitrant muco-cutaneous LP led to a rapid and prolonged clinical improvement. After 13 weeks of therapy, all the three LP patients (P1-3) showed a remarkable clinical resolution of the skin and mucosal lesions which was also reflected by a marked decrease of ABSIS scores. This was accompanied by a strong reduction of the inflammatory skin infiltrate and a marked decrease of lesional T cells and the disappearance of IL-17a+ cells underneath the BMZ. These findings provide proof-of-concept for the proposed Th1/Th17 versus Th2 dichotomy of LP versus BP and pemphigus and point towards targeting of Th2 cells as a therapeutic strategy in pemphigus and BP.

Efficacy and Safety of Risankizumab, a Selective IL-23p19 Inhibitor, in Patients with Active Psoriatic Arthritis over 24 Weeks: Results from a Phase 2 Trial

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Introduction/Objectives: To report efficacy/ safety of different doses RZB in patients (pts) with active psoriatic arthritis (PsA) over 24 weeks. Materials/Methods: In this Phase 2 study, pts with active PsA(stratified by prior TNFi and concurrent MTX use) were randomized 2:2:2:1:2 ratio to receive RZB(150mg at weeks [Wks] 0, 4, 8, 12, and 16 [Arm 1], 150mg at Wks 0, 4, and 16 [Arm 2], 150mg at Wks 0 and 12 [Arm 3], 75mg single-dose at Wk 0 [Arm 4]) or matching placebo(PBO, Arm 5). Pts completing Wk-24 visit had option to enter separate open-label extension (OLE) study; pts not entering OLE were followed until Wk-32. Efficacy assessments included ACR20/50/70, PASI, minimal disease activity (MDA), DAS28(CRP), dactylitis count, SPARCC enthesitis index, pain-VAS, HAQ-DI, and mTSS responses. Results: Of the 185 pts who received study drug, 173(93.5%) completed 16Wks of treatment;145(78.4%) entered OLE at Wk-24. Primary endpoint of ACR20 response at Wk-16 was achieved by pts in each RZB arms. At Wk-24, ACR20/50/70 responses were significantly higher in pts receiving RZB(pooled across all RZB arms) vs. PBO. PASI75/90/100 responses at Wk-24 were significantly higher in RZB-treated pts vs. PBO. At Wk-24, RZB-treated pts achieved significantly higher MDA responses and greater improvements in DAS28(CRP) and Pain–VAS. Improvements in HAQ-DI and enthesitis from BL were numerically greater in RZB arms. At Wk-24, RZB-treated pts(pooled across all RZB arms) showed significant improvement from BL in mTSS vs. PBO. Treatment-emergent adverse events (TEAEs), collected up to Wk-32, were comparable across treatment arms.; most common TEAE was infection. There were no deaths or cases of tuberculosis in RZB-treated pts; 2 adjudicated major adverse cardiovascular events were reported in RZB arms. Conclusion: Pts with active PsA treated with RZB maintained improvement in joint and skin symptoms through 24 wks. RZB-treated pts(pooled across all RZB arms) showed evidence for inhibition of radiographic progression. RZB was well-tolerated with no new or unexpected safety findings.

Weekly adalimumab (ADA) in patients with moderateto-severe hidradenitis suppurativa (HS) following loss of response (LOR), or worsening or absence of improvement (WOAI)

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Introduction & Objectives: To evaluate the response to treatment of adalimumab every week (ADAew) in patients with moderate-to-severe hidradenitis suppurativa/acne inversa (HS). ADA is the only currently available medication for the treatment of moderate-to-severe HS.Materials & Methods: This analysis includes patients with moderate-to-severe HS in PIONEER I/II who had LOR (loss of at least 50% of improvement in abscess and inflammatory nodule (AN) count achieved from baseline to Week-12 in patients who had previously achieved HS Clinical Response [HiSCR] at Week-12 in Period-A) or WOAI (no achievement of HiSCR at Week-12 in Period-A, followed by an AN count ≥ baseline AN count on 2 consecutive visits [excluding Week-12] that occurred at least 14 days apart in Period-B) after switching from ADA every-week (ADAew) in Period-A to ADAew, ADA every-other-week (ADAeow), or placebo (PBO) in Period-B, and then entered open-label-extension (OLE). Results: Fifty patients who received ADAew in Period-A switched to PBO in Period-B, experienced LOR (n=29) or WOAI (n=21), and entered OLE; 40 patients who received ADAew in Period-A switched to ADAeow in Period-B, experienced LOR (n=21) or WOAI (n=19), and entered OLE; 35 patients who received ADAew in Period-A, received ADAew in Period-B, experienced LOR (n=19) or WOAI (n=16), and entered OLE. Among patients who experienced LOR in Period-B, 60%–75% remaining in the OLE achieved/maintained HiSCR; 80%–90% achieved/maintained partial response. Among patients who experienced WOAI in Period-B, 18%–33% remaining in the OLE achieved/maintained HiSCR; 60%–70% achieved/maintained partial response. No difference in response

among Period-B treatment groups was apparent. Conclusions: Among patients who remained in OLE regardless of treatments received in Period-B of PIONEER I/II, treatment with ADAew after LOR resulted in recapture of response, and treatment with ADAew after WOAI resulted in improved partial response and HiSCR. Continuous ADAew results in less LOR or WOAI than ADAeow or PBO. These results should be interpreted with caution due to small sample size and observed case data at later visits.

Primary Results from a Phase 2b, Randomized, Placebo-Controlled Trial of Upadacitinib for Patients with Atopic Dermatitis

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Introduction/Objectives: Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by pruritic skin lesions. The selective JAK-1 inhibitor, upadacitinib, is being investigated for treatment of patients with AD and other inflammatory indications. Materials/Methods: In the first 16-week, double-blind portion of this 88-week, dose-ranging trial, adults with moderate-to-severe AD (EASI ≥16, BSA ≥10%, IGA ≥3) inadequately controlled by topical treatment, or for whom topical treatments were not medically advisable, were randomized to once-daily upadacitinib monotherapy 7.5, 15, or 30 mg, or placebo. Missing data were handled by last-observation-carried-forward (continuous variables) and non-responder-imputation (categorical variables). Results: Of the 167 randomized patients; 166 received study drug (42 in each upadacitinib dose-group; 40 in placebo). The primary efficacy endpoint, mean percentage improvement in EASI score from baseline to week 16, for upadacitinib 7.5/15/30mg groups was 39.4%/61.7%/74.4% vs 23.0% placebo

IL-38 has an anti-inflammatory action in psoriasis and its expression correlates with disease severity and therapeutic response to anti-IL-17 treatment

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Background: IL-36 cytokines, a subgroup of IL-1 family, play an important pathogenic role in psoriasis. IL-36s comprise three agonists, IL-36a, IL-36b and IL-36g, abnormally induced by IL-17 in psoriatic skin, and two receptor antagonists, IL-36Ra and IL-38, this last being yet poorly investigated in psoriatic context. Objectives: 1) to analyze skin and serum levels of IL-38, together with other IL-36 members, in affected patients before and after the biological inhibition of IL-17A with secukinumab; 2) to assess in vitro expression and regulation of IL-38 in keratinocytes (KC) and endothelial cells (EC) cultures activated with psoriasis-related cytokines; 3) to investigate the effects of recombinant IL-38 administration in vitro in human KC and EC cultures activated by inflammatory cytokines, and in vivo in the imiquimod (IMQ)-induced murine model of psoriasis. Materials and methods: 1-2) IL-38 (together with IL-36Ra and IL-36g) levels were analyzed in skin biopsies and serum of psoriatic patients before and 8-week after secukinumab treatment, as well as of healthy donors, by immunohistochemistry (IHC), real-time PCR and ELISA techniques. IL-38 mRNA and protein expression were also evaluated in human KC and EC cultures activated by IL-17, IL-22, TNF-a, IFN-g and IL-36g; 3) KC and EC cultures treated by recombinant IL-38 or IL-36Ra and activated by IL-36g were analyzed in terms of expression of inflammatory molecules, differentiation and proliferation, by Western blotting, real-time PCR and proliferation assays. For in vivo analysis, mice were topically treated with 5%IMQ and concomitantly injected with recombinant IL-38, IL-36Ra or control vehicle for 5 consecutive days. On day 6, skin biopsies were collected and analysed in terms of expression of inflammatory and epidermal architecture parameters by IHC. Results: 1) We found reduced IL-38 skin levels in psoriatic patients and in other skin diseases characterized by neutrophilic infiltrate. The balance of IL-36g /IL-38 serum levels in psoriatic patients was sharply in favor of agonist and was associated with disease severity, evaluated in terms of Psoriasis area and severity index. Treatment with secukinumab led to IL-38 upregulation in skin and serum of psoriatic patients, with a positive correlation with the therapeutic efficacy. 2) IL-36g, IL-17 and IL-22 cytokines, triggering de-differentiative programs in KC, downregulated IL-38, whereas induced the expression of other IL-36 members. 3) Recombinant IL-38 counteracted the biological processes induced by IL-36g in

KC and EC cultures, and attenuates the severity of the psoriasiform phenotype induced by IMQ in mice, by restoring the KC proliferation and differentiation programs, and reducing the inflammatory infiltrate. Conclusions: IL-38, a cytokine with a protective role on skin homeostasis, has strong anti-inflammatory effects in psoriasis and represents a valid biomarker for responsiveness of patients to anti-IL-17 therapy.

Apremilast in real practice: experience and learnings from our 100 patients serie

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Introduction Psoriasis is a noncommunicable, painful, disfiguring and disabling disease for which there is no cure and with great negative impact on patients' quality of life (QoL). The need for treatment is usually lifelong. It is also very important to identify and manage common comorbidity that already exists or may develop, including cardiovascular and metabolic diseases as well as psychological conditions. These comorbidities make the management of psoriasis difficult in the long term. Topicals, conventional systemics, apremilast and biologics are therapeutic options available to treat psoriasis patients. Apremilast is an oral PDE4 enzyme inhibitor capable of blocking leukocyte production of IL-12, IL- 23, TNF-α, INF with subsequent suppression of Th1 and Th17-mediated immune responses. This drug was approved in 2016 in Spain as a new treatment option with different positioning according to the region. This positioning makes experience conditional on the patient profile selected. Matherials and Methods * We present our 100 patients serie, some learnings about this drug management and the therapeutic algorithm evolution. Conclusions * The treatment with apremilast improved the cutaneous and systemic symptoms (itch, pain, …). Our experience shows better results on moderate psoriasis patients, leading to a change in the treatment algorithm. The iconography demonstrates the effectiveness in these patients.

POSTER SESSION

1. Long-term immunomodulatory treatment of hidradenitis suppurativa: practical insights

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Introduction and Objectives: Hidradenitis Suppurativa (HS) is a recurrent disease characterized by a progression of asymptomatic nodules to deep-seated lesions and sinus tracts with subsequent scarring. The development of PIONEER I and II controlled trials demonstrated that Adalimumab, a humanized monoclonal antibody targeting TNF-alpha pathway, is a highly effective drug for the reduction of inflammatory lesions over a 12 weeks period. To our best knowledge, data on the long-term management of HS patient receiving adalimumab are scarce. The aim of our single centre retrospective study, was to review the clinical data of HS patients receiving adalimumab therapy and analyse the therapeutic response, adverse effects, duration and reasons of short suspension periods (SSP) in the group of HS patients receiving anti-TNFα therapy for at least 12 months. Methods: All the medical records of HS patients receiving adalimumab therapy were reviewed. Patients receiving adalimumab therapy for at least 12 months were selected (LT-group). Disease severity assessments using Hurley stage, modified Sartorius score (mSS), International Hidradenitis Suppurativa Severity Score System (IHS4) score and HiSCR50 response rates to treatment were calculated at the beginning of the adalimumab therapy and at 12, 24, 36, 48 (± 4) weeks. VAS (Visual Analogue Scale) pain score was retrieved at the beginning and after 48 weeks of adalimumab therapy. The length and the causes of any anti-TNFα short suspension periods (SSP) were analysed. Results: Average mSS before receiving adalimumab therapy was 94.7, median Hurley stage was 3, IH4 stage was severe in 64.7% and moderate in 35.3%. In the LT-group, a significant decrease of inflammatory lesions after three months of therapy was observed, with 60% of patients achieving HiSCR50 response. During therapy, mSS decreased from 88.5 to 51.5 and IH4 values decreased from 26.6 to 13.1. Interestingly, the remission of disease severity observed at 3 months was maintained at 6, 9 and 12 months. All patients experienced at least one SSP, which lasted 16.2 days on average. The major cause of SSP was flu or other concurrent HS independent infections (66.3%). The remaining 43.7% were associated with the occurrence of HS inflammatory phenomena. In the LT-group no serious adverse events were registered. Conclusions: Long-term adalimumab therapy for HS evidenced overall positive clinical results at 3 months, which were maintained at 12 months, without serious adverse events. In our experience SSPs were common events during HS recrudescence episodes requiring additional adequate therapeutic interventions.

2. Hidrosadenitis suppurativa: Two-phenotype classification with twostep cluster method

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Introduction: Phenotypic classification of hidradenitis suppurativa (HS) has been repeatedly attempted by diverse statistical methods. The most widespread classification was described by Canoui-Poitrine after latent class analysis (LCA) and comprises three phenotypes. Materials and methods: In a series of 410 patients from our hospital we applied a clustering technique called TwoStep cluster method in order to obtain a phenotypic classification. It is a scalable cluster analysis algorithm designed to handle very large data sets, and it can handle both continuous and categorical variables. It can also automatically select the number of clusters. We included in the model a set of variables including sex, age of onset, localization and type of HS lesions, tobacco use, Severity scales (Hurley, HS-PGA and IHS4) and body mass index (BMI). Calculations were performed with SPSS 17. Results: The results yielded the presence of two clusters, C1 and C2. C1 comprised 27,2% of the patients, being more frequently women with higher BMI, later onset and lesions involving axillar region. C2 comprised 72,8 % of the series, and was predominant in male patients with low BMI, frequent involvement of head, neck, trunk, gluteal and groin areas, and earlier onset. Conclusions: HS can be clinically polymorphic, reflecting a different pathophysiology that can be related to genetics, lifestyle or a combination of both. In our setting, the classification in two phenotypes seems to better reflect the clinical pattern of the patients, and can aid to better diagnosis and tailored management.

3. The heterogeneity of hidradenitis suppurativa and responses to therapy

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Introduction: Hidradenitis Suppurativa (HS) is a chronic, painful, autoinflammatory condition resulting in nodules, abscesses, and sinus tracts. Commonly affected sites are apocrine-gland bearing areas including the axillae, groin, buttocks and submammary regions. Typically HS starts after puberty, persists for many years and worsens over time. Patients experience significant physical and psychological morbidity. Early diagnosis and treatment is imperative to aid management of symptoms and prevent progressions of the disease. HS is closely associated with disease modifying comorbidities including the metabolic syndrome, androgen dysfunction, and smoking. Phenotypic heterogeneity is now recognised in HS. Materials/Methods: A review was undertaken of entries in the local HS registry database with specific analysis undertaken phenotype categories and associated comorbidities. Descriptive characteristics, two sample t-tests and chi-square analysis were used to analyse the data. Results: The four phenotype classification categories identified included: (1) Early paediatric onset group; (2) male group; (3) female group; and (4) genetic group. Characteristics of group 1 included: early onset disease; classic presentation in groin and axillae; and latent issues with metabolic comorbidities including insulin resistance, poly cystic ovarian syndrome (PCOS), and weight (overweight not obese). Characteristics of group 2 included: presentation of predominantly posterior disease especially buttocks; current smokers; visceral adiposity rather than central adiposity; associated hyperlipidaemia; and eventually seem to "burn out". Characteristics of group 3 included: classic presentation of axillary and inframammary lesions; and prominent metabolic comorbidities including obesity, insulin resistance, hyperlipidaemia and PCOS; and high levels of psychological stress. Characteristics of group 4 included: positive family history of HS; extensive, severe, and widespread disease; and association of syndromal conditions. Discussion: Our local HS clinic experience agrees with Latent Class subtype classification, with the proviso that other authors have not included a group presenting in the pre-pubertal years nor the rare hereditary syndromes of which HS is a component. Phenotype targeted therapy may be useful in HS. At this meeting an update of our results of therapy using the subclassification will be presented.

4. Hidradenitis suppurativa and biologic therapy: efficacy and safety in surgery

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Introduction Adalimumab aproval for the treatment of moderate and severe variants of hidradenitis suppurativa (HS) has become an important advance for this condition. There is some controversy about the need of biologic therapy discontinuation in those cases where a surgery is indicated. This is justified by a posible increase of complications mainly related with infections. Focusing on HS, there is a high interest in not withdrawing the biological therapy, given that the expected results of the surgery could be better. The hypothesis, that is widely accepted by the general and

dermatologic surgeons, is that a patient with a well controlled inflammatory activity before, during and after the intervention will reduce immediate and late surgical complications, offering the best results in the HS management. We present a retrospective study with the aim of assessing the efficacy and safety of TNF-α blockers in a case series of patients with moderate or severe HS with fascio-cutaneous flap surgical indication to cover wide wounds related with the cutaneous disease that continued with the biological therapy along the process. Material and Methods We included all the HS patients under biological therapy that were surgically treated with indication of complex flap to remove complex fistulas after achieving a HiSCR between 2016-2018 from our Department. Results 8 patients were included, 7 males and 1 female with ages between 34 and 65 (adalimumab 7 cases, infliximab 1 case). Surgical locations were: axillae (4 cases), buttocks (2 cases), and inguinal and thigh in another patient. All of them remained under treatment with antiTNF-α and maintained HiSCR after surgery, with a median follow up of 15 months. Only one patient that discontinued treatment with adalimumab because he required a stoma in order to avoid infection. After 3 months, because of the development of new flares, Adalimumab was reintroduced and HiSCR was achieved after 12 weeks. During the short follow-up during the next 4 weeks after surgery, 3 patients had surgical wound deshiscence without infection; 2 cases were managed with conservative measures to promote second intention healing and 1 case underwent a minor surgery. No long-term complications were detected. Discussion and Conclusion Although it is necessary to individualize each case, along with our experience, we support the continuation of antiTNF-α therapy in those patients with HS who will undergo any cutaneous surgery.

5. New onset lupus nephritis during ustekinumab therapy for psoriasis in patients with and without prior systemic lupus erythematosus

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Importance: We report the development of lupus nephritis in 3 patients treated with ustekinumab for psoriasis. Objective: To report patients with psoriasis who developed new onset of lupus nephritis while on ustekinumab and to review the literature with regards to paradoxical worsening of B cell mediated autoimmunity in patients treated with ustekinumab. Design, Setting, and Participants: Case series of 3 patients with psoriasis who developed lupus nephritis with ustekinumab treatment and literature review. Interventions/Exposure: Patients were treated with ustekinumab for psoriasis/psoriatic arthritis. Main outcomes and Measures: All 3 patients developed new onset lupus nephritis. Two patients had concomitant small vessel vasculitis. Ustekinumab was discontinued in 2/3 patients. Results: Three patients with psoriasis (median age 37 years) developed new onset lupus nephritis with or without small vessel vasculitis and vasculopathy while on ustekinumab treatment for psoriasis (median time from ustekinumab initiation 17 months, range 3- 24 months). Two patients had prior systemic lupus erythematosus (SLE). All patients received treatment with cyclophosphamide and or mycophenolate mofetil (MMF) along with discontinuation of ustekinumab in 2/3 patients. Lupus nephritis resolved in 2 cases but resulted in end stage renal disease in one patient. Literature review revealed prior cases of cutaneous small vessel vasculitis and immune-bullous diseases occurring in patients on ustekinumab. Conclusions and Relevance: Co-existence of psoriasis and SLE is not uncommon. Ustekinumab is an effective treatment for psoriasis, including in the setting of concurrent SLE. However, development of B cell mediated auto-immunity has been reported in patients treated with ustekinumab. This case series highlights a possible association between ustekinumab and the development lupus nephritis and vasculitis/vasculopathy in patients with or without prior diagnosis of SLE.

6. Lupus comedonicus: an atypical and rare presentation of chronic cutaneous lupus erythematosus

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A 55-year-old woman presented with one-year history of asymptomatic erythematous papules, closed and open comedones on the right side of her chin, in association with marked solar elastosis of the surrounding skin. Histopathology showed follicular dilations, sometimes with cystic appearance, vacuolar degeneration of the epidermal basal layer, a modest lichenoid infiltrate and copious intradermal deposits of mucin. PAS staining revealed thickening of the basement membrane, more pronounced around the hair follicles. The immunophenotype documented the presence of a fair number of plasmacitoid dendritic cells (CD123) in the perifollicular lichenoid areas. These findings were consistent with a diagnosis of comedonicus lupus, a rare variant of chronic cutaneous lupus erythematosus described by Haroon and Fleming in 1972. Routine laboratory investigations and autoantibody profile were within normal limits and the patient had no systemic symptoms.

7. PD-1 rs2227981 polymorphism analysis in patients with systemic sclerosis

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Introduction and objectives Given the expanding clinical use of PD-1 inhibitors, immune related adverse events are increasingly reported. Interestingly some cases of scleroderma developed after treatment with PD-1 inhibitors have been recently reported. The gene coding for PD-1(PDCD1) presents several polymorphisms. Significant associations between PD-1 rs2227981 polymorphism and cancers are present. Recent studies have shown that polymorphisms of PDCD1 can be associated with various autoimmune diseases. The aim of this study was to evaluate the prevalence of the functional polymorphism rs2227981 of the PD-1 gene in patients with systemic sclerosis and healthy controls, in order to suggest a possible susceptibility to the disease by this mutation. Material and methods A cross-sectional study was conducted among 69 patients affected by systemic sclerosis and 75 healthy controls referred to Padua University Hospital. DNA extraction was performed from peripheral blood nuclear cells through Easy-DNA Kit (Invitrogen). Isolated DNA was amplified by PCR and PD-1-rs227981 polymoprhism was genotyped using StepOnePlus Real-Time PCR system (Applied Biosystem Foster City, CA). Statistical analysis was performed using SAS software package and data were analyzed using the Pearson's chi-squared test. The odds ratio with 95% confidence interval (95% CI) and a p value 0.05). The frequency of the two genotypic structures containing the minor allele T(TT+CT genotypes) has also been compared with the homozygous wild-type genotype(CC). The frequency of the T genotypes was found to be 62.3% in the patients and 74.7% in the controls (p>0.05). Conclusions The results obtained are not consistent with the presence of an association between the polymorphism rs2227981 and a greater susceptibility to the development of systemic sclerosis. Analysis of other PD-1 polymorphisms could be useful to assess the possible role of PD-1 in the pathogenesis of this autoimmune disease.

8. Nivolumab induced morphea

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Therapies that activate the immune system are revolutionizing the care for patients with cancer. These therapies block immune checkpoints, such as monoclonal antibodies against programmed cell death-1 (PD-1) and potentiate T cell responses, including anti-tumor responses,. The side effects of anti–PD-1 therapies are generally mild and related to autoimmune reactions. Here we present the case of a 70-year-old woman with metastatic melanoma of the scalp receiving nivolumab 3 mg/kg administered intravenously every 2 weeks for 12 cycles. She developed violaceous plaques with centrifugal expansion in submammary and inguinal regions, punch skin biopsy confirmed a morphea. The patient was treated with systemic steroids with progressive resolution of the lesions within 30 days.

9. T-cell responses against autoantigens of the skin in patients with lichen sclerosus

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Introduction: Lichen sclerosus (LS) is a rare inflammatory skin disorder affecting mainly mucous membranes of the anogenital area, although others parts of the skin can also be involved. Its pathogenesis is still unclear. Previous studies suggested a pivotal role of pathogenic T cells mainly shifted towards an interferon-gamma (IFN-γ)-producing T helper (Th)-1 phenotype. Like lichen planus, the histopathology of LS shows an interface dermatitis, with linear arrangement of T cells along the basement membrane zone (BMZ), suggesting a potential T cellular recognition of autoantigens in the epidermis or BMZ. Objectives: To characterize the T cell response against autoantigens involved in the pathogenesis of autoimmune blistering disease (AIBD) in patients with LS and to evaluate differences in the T cell response between genital and extragenital LS. Materials & Methods: A total of 11 patients with LS, confirmed by histopathology, and 10 healthy controls (age- and sex-matched), that were consecutively referred to our department, were included. Peripheral blood mononuclear cells (PBMC) were isolated and and co-cultured in vitro with the bullous pemphigoid (BP)180 antigen (NH2- or COOH-terminal ectodomains), desmoglein 3 and collagen VII. Subsequently, the frequency of antigen-specific T cells producing IFN-γ (Th1), interleukin (IL)-5 (Th2) and IL-17A (Th17) was determined

by ELISpot assay in patients and HC. Furthermore, paraffin-embedded skin and mucosa sections from LS patients were stained for CD3, CD4, T-bet, GATA3 and IL-17A in order to compare the profile of the cutaneous inflammatory infiltrate. Results: Preliminary results show that LSA patients harbour a T-cell response against AIBD antigens, in particular against BP180. No differences seem to exist between genital and extragenital LS. The observed peripheral blood T cell response is prevalently Th1-mediated, paralleling the predominance of Th1 cells in the inflammatory infiltrate found in LS lesions. Although mucosal and skin lesions did not show a marked IL-17A+ cellular infiltrate, a subgroup of LS patients showed a significant Th17 response against AIBD antigens in the peripheral blood. Limitation: Small sample size; retrospective collection of skin and mucosal biopsies Conclusion: BP180 and additional cutaneous autoantigens may play a role in the pathogenesis of LS. Whether they may be involved in the developmental phase of LS pathogenesis or rather in perpetuating, chronic inflammatory stage is yet to be elucidated.

10. Dermatomyositis: rare clinical variants

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Introduction: Dermatomyositis (DM) belongs to a group of rare autoimmune diseases which is characterized by skin rashes and myopathy at variable degrees. Since the initial classification of Bohan and Peter, our knowledge regarding diagnostic procedures and criteria, and the correlation of clinical phenotypes with immune serological abnormalities has largely improved. The diagnostic hallmark of DM is the characteristic heliotrope rash, Gottron papules and weakness of the proximal muscles. MRI and muscle biopsies are mandatory to confirm the diagnosis of DM. Along with pathognomonic, characteristic and compatible cutaneous features, several uncommon and rare skin manifestations have been described. It has been reported that up to 20% of DM patients lack muscle involvement or show subclinical myopathies. These patients are classified under the umbrella “clinical amyopathic DM” (CADM). Wong-Type DM (WTDM) is a rare clinical subset of DM, characterized by the coexistence of DM and cutaneous features of pityriasis rubra pilaris such as hyperkeratotic, erythematous, follicular confluent papules on the backs of the hands, arranged in a linear way over the bony prominences. The association of adult DM with malignancies is not so rare, the most commonly associated neoplasms are lymphomas, lung cancer, gastrointestinal and gynecologic tumors. Therapeutic options include immunomodulatory agents such as high-dose immunoglobulins, systemic glucocorticoids and immunosuppressive adjuvants, including azathioprine, and methotrexate, cyclosporine and rituximab. Aims: To describe rare clinical variants of DM which are associated with novel serological markers, including DM associated to anti-nuclear matrix protein-2 antibodies and anti-aminoacyl-transfer RNA synthetase antibodies. Furthermore, we will focus on peculiar clinical features of DM, including WTDM, CADM, and paraneoplastic DM. Methods: We reviewed the German-language and the English-language scientific literature using the key words “dermatomyositis”, “auto-antibodies”, and “clinical features” alone or in combination, focusing on particular cutaneous signs and their association to peculiar auto-antibodies subsets. Results: We showed the correlation between unusual antibodies profile and rare clinical features. In addition, we re-evaluated the association between neoplasia and DM according to epidemiology and clinical picture, including the intriguing case of WTDM and considering the lack of guidelines about the cancer screening in DM. Conclusion: DM is known for its polymorphous skin manifestations. Several subsets of auto-antibodies have been described, that correlate with different clinical cutaneous and systemic features. The association between DM and neoplasia should be re-evaluated, taking into account the prevalence of DM in different countries and the antibody subsets, although a thorough cancer screening is mandatory.

11. Successful treatment of Miescher’s cheilitis in Melkersson-Rosenthal syndrome

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Melkersson-Rosenthal syndrome (MRS) is a rare, noncaseating granulomatous disease consisting of persistent or recurrent orofacial edema, relapsing peripheral facial paralysis and fissured tongue . Oligosymptomatic and monosymptomatic forms are more common than the complete triad . Persistent or recurrent lip swelling is known as Miescher syndrome. We report a case of a 55-year-old woman who presented with 10-year history of swelling of upper and lower lip and fissured tongue. Labial mucosa biopsy showed non-necrotizing giganto-epithelioid granuloma. Diagnosis of Melkersson-Rosenthal syndrome was retaind because of association of cheilitis and lingua plicata. In our case we excluded Crohn’s disease and endocrinopathies. She was treated with oral steroids and intralesional injections with triamcinolone without any improvement. She failed to respond to methotrexate, doxicicline and azathioprine. Finally the patient improved with a new treatment without side effects or pain.

12. Multiple unhealing ulcers in an otherswise healthy patient

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A 49 year-old male patient with no relevant previous clinical history was referred to our department,for the recent onset of multiple small papules which later evolved into several ulcers on both flanks, pubis and sub-mammary folds. Laboratory findings revealed mild neutrophilia, while the remaining tests - including liver and kidney function tests, electrolytes and urinalysis - were within the normal range. A lesion border biopsy was performed, which showed loss of corneous and granulous epidermal layers with resulting small areas of ulcerations and a marked inflammatory infiltrate at the dermal-epidermal junction consisting of lymphocytes, mature plasma cells, occasional giant cells and numerous neutrophils. The clinical and laboratory findings, together with the suggestive histological examination, pointed toward a diagnosis of pyoderma gangrenosum. The patient was therefore successfully treated with methotrexate 15 mg/day (associated with folin) and decremental doses of prednisone. Pyoderma gangrenosum (PG) is an ulcerative cutaneous condition of uncertain etiology. Since there are no specific diagnostic laboratory test or histopathologic features, other causes of ulceration and treatable associated diseases need to be excluded. Diagnostic work-up should hence include careful history, physical examination, skin biopsy to exclude panniculitis and infections, hematologic studies (full blood and platelet count), serologic studies, urinalysis, chest X-ray and GI and liver function investigations as clinically warranted. The mainstay of treatment is long term immunosuppression, often with high doses of corticosteroids or low doses of cyclosporine. Second line therapies include antibiotics, corticosteroids, immunosuppressive agents, and biologic agents.

13. Well's syndrome and atopy in childwood: a case report

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Well's syndrome, or eosinophilic cellulitis, is a rare, recurrent disorder. Acute erythematous and edematous plaques, resembling bacterial cellulitis, characterize it and bullous lesions are uncommon, especially in childhood. The pathogenesis is not well defined, one hypothesis is that it represents a hypersensitivity mechanism, some of the few pediatric reports shown a possible association with atopy. We present a pediatric case of bullous Wells syndrome. A 2 year-old boy presented with edematous erythematous papules and plaques and bullae, associated with erosion covered by yellowish crust, on his face, neck and extremities. He was afebrile and the skin lesions were pruritic but not tender. Similar lesions were recurrent since the age of 7 month. Medical history included atopic dermatitis, food allergy and asthma. A skin biopsy was performed, showing superficial and deep dermal infiltrated with predominance of neutrophils and eosinophils, flame figures and some palisading histiocytes around flame figures. On the basis of morphologic and histopathologic feature a diagnosis of Wells' Syndrome was made. Lesions resolved spontaneously, but a recurrence occurred six month later. This was treated with topical and systemic steroids with benefit. The pathogenesis of Wells' syndrome is not well defined. It has been suggested a type IV hypersensitivity reaction to various endogenous and exogenous stimuli. A pediatric case series reported a higher proportion (63%) of atopic patients compared to general population. This unusual background could explain the onset of hypersensitivity reaction with eosinophils. In literature 65 pediatric Wells syndrome are reported and in most of them information about atopic disease is not available (54% - n=35). Our case report adds data about this topic and seems to confirm this association.

14. Neuro Sweet syndrome

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Introduction: Sweet's syndrome (SS) is an inflammatory disease characterized by fever, leucocytosis and skin lesions that histologically consist of a dermal infiltrate of neutrophils with nuclear fragmentation. Aseptic neutrophilic inflammation may occur in organs other than the skin. Central nervous system involvement in SS, Neuro-Sweet's syndrome (NSS), is rare and reported especially among Asian patients. Objectives: We performed a systematic review of the literature to find articles reporting cases of SS with neurological involvement. Matherials and Methods: The search terms: "Sweet's syndrome/disease with neurological involvement, Neuro Sweet Syndrome/Disease" were used in the Pubmed Database. Conclusions: Sixty-nine NSS patients including 46 males and 23 females, more Asian than Caucasian, have been described from 1983 to date. The average age was 48.7 year-old. The most representative neurologic symptom was the altered state of consciousness, followed by headache and memory disorders. Differently

from SS with skin or other district involvement, NSS appears to be more common in Asian patients than in Caucasian ones and affects mainly the male sex in the third or fourth decade of life. A very wide range of symptoms and signs can occur, depending on which part of the nervous system is affected. Initial presentation is usually with the SS typical skin lesions (erythematous infiltrated plaques) followed by neurological involvement. However, also an opposite presentation or a simultaneous skin and nervous system involvement may happen. One of the 69 cases of NSS described in the literature, was an our female patient who, after 4 years from the diagnosis of SS, developed right arm involuntary movements and paresthesias. According to clinical history, neurologic presentation, and neuroimaging, NSS was diagnosed and the patient obtained a cutaneous and neurological remission with a steroid and cyclosporine therapy. Awareness of the possible neurological complications in SS is important to avoid unnecessary therapies for other forms of meningoencephalitis and lead to successful treatment with systemic corticosteroids.

15. Off-label use of 4-4'-diaminodiphenylsulfone

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Introduction Dapsone (4,4'-diaminodiphenylsulfone) has antimicrobial and antiprotozoal effects by inhibiting folate synthesis, and also anti-inflammatory features similarly to non-steroidal anti-inflammatory drugs. For this reason it is used in several dermatologic diseases, as a systemic agent and as a topical agent in acne vulgaris. Before starting drug adminstration it is necessary to check some blood tests, like CBC, glucose 6-phosphate dehydrogenase, lactate dehydrogenase, iron count, indirect bilirubin count, transaminases and methemoglobinemia. This screening is necessary in order to try to avoid possible adverse reactions, such as haemolysis, agranulocytosis, anemia, abdominal pain, isolated abnormalities of liver function tests, hypersensitivity syndrome with hepatic coma. Objectives Dapsone is the first choice in the treatment of dermatitis herpetiformis, erythema elevatum et diutinum, acropustulosis infantilis, prurigo pigmentosa and subcorneal pustular dermatosis (Sneddon-Wilkinson disease). Anyway, for its mechanisms of action acting on inflammatory pathways, dapsone could be used for every skin immune mediated inflammatory disease. Matherials and methods We shortly focused on some reports about off-label uses of dapsone in English literature. Conclusions We found administration of dapsone with no relevant side effects in various dermatologic diseases, such as disseminated granuloma annulare, Behcet's disease, alopecia areata, Wells syndrome, pemphigoid gestationis, pustular psoriasis, lichen planus pemphigoides, granulomatous rosacea, Kaposi sarcoma, pityriasis rosea, Hallopeau's disease, Hailey-Hailey disease, mucinosis, Grover's disease, nocardiosis, lymphomatoid papulosis, and so on. To now, even if properly controlled trials showing efficacy are lacking, dapsone remains a valid option in the treatment of refractory cases of these diseases.

16. Schnitzler's syndrome: a case without monoclonal gammopathy

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Schnitzler syndrome is a rare autoinflammatory disease characterized by a chronic recurrent urticarial eruption and monoclonal gammopathy. We present a 21-year-old female with a 3-years-old history of chronic urticaria, hand and foot arthralgias, myalgia, intermittent fever, for which was referred to the rheumatology unit. Empirical treatments with antihistamines and steroids were administered, without significant improvement. Little benefits derived from cyclosporine 3.5 mg/kg/die; disappointing also a 6-month cycle with Omalizumab. After a new severe urticarial eruption a skin biopsy was performed, with the detection of perivascular infiltrate of neutrophils with leukocytoclasia at the histology; cryoglobulins and elevated systemic inflammatory marker were the only abnormal finding in the blood. Finally, a diagnosis of Schnitzler syndrome was made. Although the typical form of Schnitzler's syndrome exhibits the presence of monoclonal gammopathy as a diagnostic criterion, monoclonal gammopathy may be absent in an atypical form. The patient was started on Anakinra 100 mg subcutaneous daily, obtaining an immediate and striking response.

17. Late-onset cryopyrin-sssociated periodic syndrome due to myeloid-restricted somatic NLRP3 mosaicism

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Objective. To identify the cause of disease in an adult patient presenting with fevers, chills, urticaria, fatigue and myalgias as well as nephrotic range-proteinuria in addition to fecal incontinence due to amyloidosis. Material and Methods: We studied a 61-year-old patient, who was born from a nonconsanguineous twosome of Spanish descent; there was no family history of CAPS. Her main previous pathologies included Anquilosing Spondylitis, which was diagnosed in 2014, and for that reason she was put on TNF antagonist´s treatment such as Adalimumab, Golimumab. The last one was Certolizumab that limited improvement of dermatology lesions. Nevertheless, help with inflammatory back pain. This treatment was ruled out in 2017; in order to start with IL inhibitor. Beside that, she suffered from uterous cancer with hysterectomy.in 1995 In 2010 she was diagnosed by bilateral neurosensorial hearing loss and papilledema. In 2015 fecal Incontinence was diagnosed, no triggering factors were identified, signs and symptoms including low-grade. fever, conjunctivitis, polyarthralgias, and oligoarthritis affecting knees, wrists, elbows, and ankles, appeared 1 year later. At the age of 40, she presented with recurrent episodes of urticaria-like rash (figure 1) fever, conjunctivitis, and oligoarthritis at age 56 , 3 years later she developed fecal incontinence as well as 12 g of proteinuria with also high levels of Amyloidosis. For that reason it was suspected that the patient had a variant of Muckle Wells Sindrome , although screening in a commercial laboratory was found a somatic mutations in NLRP3. IL.1 as well as IL 1B Inhibitors treatment resulted in a positive response. The first one had a partial response (Figure 2), so we switched to the second one with fully dramatic positive response (Figure 3) Conclusion. We identified the novel gain-of-function NLRP3 mutation, which was detected as a somatic mutation restricted to myeloid cells, as the cause of late-onset but otherwise typical CAPS., including these starting during adulthood

18. Therapeutic value of BP180 autoantibody titres in patients with bullous pemphigoid

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Introduction: In bullous pemphigoid (BP), an autoimmune blistering disease, serum levels of autoantibodies against BP180 correlate with disease activity. Treatment of BP can be challenging as it has a tendency to relapse and occurs mainly in elderly patients with comorbidities. No consensus exist on how BP treatment strategies should be guided: based on disease severity or guided by repeated measurements of BP180 titers. Objectives: We investigated whether BP180 can help to outline a treatment strategy and whether it is useful to predict remission. Materials and Methods: This retrospective study enclosed patients with proven BP between January 2005 and December 2016 at the Department of Dermatology at Ghent University Hospital. A total of 60 patients with BP were included and were grouped according to the need for immunosuppressive therapy (systemic corticosteroids, methotrexate, mycophenolate mofetil, dapson, azathioprine) or non-immunosuppressive (topical corticosteroids +/- tetracyclines). BP remission was defined as complete disappearance of blisters for more than 3 consecutive months. Results: Baseline BP180 levels were significantly linked with clinical severity (mild:

19. Monitoring of autoreactive T cell responses in autoimmune bullous diseases

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Introduction: Autoimmune bullous diseases (AIBD), including pemphigus vulgaris (PV), pemphigus foliaceus (PF) and bullous pemphigoid (BP) are rare skin diseases in which circulating autoantibodies cause blisters of the skin and/or mucous membranes. Autoreactive T cells that react against disease-specific autoantigens (i.e. desmoglein (Dsg)1 and 3 in PV and PF, BP180 in BP) are crucial for disease pathogenesis providing essential B cell co-stimulation for the development of pathogenic autoantibodies. Thus, detection of autoreactive T cells in AIBD is of particular interest to monitor disease progression and response to treatment. Objectives: To evaluate read-outs for the detection of antigen-specific autoreactive T cells in patients with pemphigus and BP. Material and Methods: A total of 16 patients with PV, 5 patients with PF and 23 patients with BP were included, 20 age- and sex-matched healthy individuals served as controls. Peripheral blood mononuclear cells (PBMC) were isolated from peripheral blood and were co-cultured with Dsg3, Dsg1 or BP180 recombinant antigen to induce autoreactive T cell activation. The T cell response was subsequently evaluated by means of ELISpot or 3H-thymidine incorporation assay. Dsg3-peptide-specific T cells, reactive against known immunodominant epitopes of Dsg3 were further analysed in a subgroup of PV patients. Conclusions: Autoreactive T cells against Dsg3 or Dsg1 were predominantly detected in patients with PV and PF. In

contrast, reactivity against BP180 was mainly observed in patients with BP. The autoreactive T cell response was markedly Th2-mediated as the majority of T cells secreted interleukin-5 upon antigen-stimulation whereas a significant interferon-gamma-mediated T cell response could not be observed. In PV patients with the prevalent HLA-DRB1*0402–haplotype, reactivity against Dsg3 coincided with a low-frequent T cell response against a set of 5 previously described immunodominant Dsg3-peptides that could be further enhanced by repetitive stimulation with Dsg3. Of note, topical treatment with clobetasol of a subgroup of BP patients led to a significant reduction of peripheral blood autoreactive T cells strongly suggesting a systemic effect of topical glucocorticoids. In summary, we show that autoreactive T cells from patients with pemphigus and BP can be readily detected ex vivo by ELISpot assay. Our analyses provide further evidence for a crucial role of Th2 cells in these autoantibody-mediated disorders. Monitoring of autoreactive T cells in patients with PV and BP holds major promise as a helpful tool for disease evaluation.

20. Pretibial dystrophic epidermolysis bullosa: a case report

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A 52-years-old man presented with bilateral, well-defined, very itchy and erythematous-violaceous plaques with some areas of erosions localized on his shins resulting from a local trivial trauma. All his toenails were dystrophic. The histological examination revealed a subepidermal blister, the direct immunofluorescence on the skin perilesional tissue for the detection of antibodies was negative and the detection of serum antibodies anti Desmogein 1, 3 and BP 180, 230 was negative. The genetic testing for mutations in the COL7A1 gene identified a genetic variant c.6832G>A on heterozygosity of the gene that defines the proteic variant p.Gly2278Arg. These data supported the diagnosis of pretibial dystrophic epidermolysis bullosa. This is a rare form of localized dystrophic epidermolysis bullosa, characterized by skin fragility with recurrent blistering and scarring plaques occurring predominantly in the pretibial area. Pruritus and nail dystrophy, especially of the toenails, is also present. Often there are no clinical abnormalities at birth, and the disorder may only appear after several years. Most cases show autosomal dominant inheritance, although recessive and sporadic cases have been described. Differential diagnosis include others inflammatory diseases such as localized bullous and lichenoid dermatoses, prurigo nodularis and dermatitis artefacta. There is no effective treatment for pretibial EB, the management remains symptomatic and includes use of protective non-adherent dressings, minimization of trauma and treatment of secondary bacterial infections. Other forms of cell, gene, protein, and drug/small molecule therapy may be available in the future.

21. Efficacy of anti-IL-17A secukinumab in acute generalised exanthematous pustulosis

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Introduction Acute generalised exanthematous pustulosis (AGEP) is a potentially life threatening drug reaction characterized by a pronounced neutrophilic skin infiltrate and disseminated pustules. In the biologics era, AGEP treatment remains still empirical, based on the administration of topical or systemic steroids in absence of true effectiveness data. Since the molecular mechanisms driving the cutaneous infiltration by the immune cells have been almost fully cleared in the last years, patients suffering from potentially life threatening forms may nowaday benefit from more effective targeted approaches. Objectives To evaluate the efficacy of IL-17A inhibition in a patient poorly responding to steroid therapy Method We treated a 63-year-old patient with AGEP who experienced major clinical improvement upon single treatment with the anti-interleukin (IL)-17 monoclonal antibody, secukinumab. The patient developed a progressive pustular rash leading to erythroderma accompanied by high fever and increased serological inflammatory markers upon treatment with the antifungal agent, terbinafine. Despite systemic treatment with prednisolone, the rash persisted and the patient's overall condition deteriorated. In light of the high expression IL-17 in the lesional skin of AGEP patients, we decided to start a single shot therapy with 300 mg secukinumab, a monoclonal antibody which selectively binds IL-17A. Within 24 hours, the clinical symptoms dramatically improved as did itching and fever. Accordingly, prednisolone was quickly tapered and stopped within 3 days. Skin biopsies taken before and after secukinumab showed a striking decrease of CD15+ neutrophils and the disappearance of the IL-17A+ skin infiltrate. Conclusion Our successful attempt to treat AGEP with an IL-17A inhibitor, strongly suggests that a) IL-17 plays a major role in the pathogenesis of AGEP and b) short term treatment with secukinumab may be a therapeutic option in recalcitrant cases.

22. Efficacy and safety of Omalizumab in patients affected by several comorbidities: data from real-life clinical practice

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Introduction and objective: To assess Omalizumab efficacy and safety in a heterogeneous population of patients affected by Chronic Spontaneous Urticaria (CSU) and several comorbidities in a real-world setting. Materials and methods: Patients affected by CSU (UAS-7 score >16) who underwent at least 4 weeks of treatment with nonsedating H1-antihistamines and were still symptomatic were treated with Omalizumab 300 mg injection as add-on to H1-antihistamines administered every 4 weeks for 6 months, followed by an 8-week treatment interruption. In case of recurrence of symptoms a second cycle of five additional doses of Omalizumab 300mg every 4 weeks (5 months) was administered (total treatment duration 13 months). Clinical assessment of UAS-7, DLQI and blood tests were performed at baseline, 12 weeks (W12), 24 weeks (W24) and 52 weeks (W52) of treatment. Response was assessed based on reduction of UAS-7. Results: 25 patients (9M and 16F mean age 54,16) affected by CSU were enrolled. Comorbidities affecting our study population were divided into four categories: cardio-metabolic (68%), oncologic (24%), infectious (16%), allergic (56%) and immunologic (40%). In particular, cardio-metabolic comorbidities were arterial hypertension (24%), dyslipidemia (16%), severe osteoporosis (8%), lower limb ischemia (4%), diabetes (4%), hepatic steatosis (4%), tachycardia (4%), ischemic cardiomyopathy (4%); oncologic comorbidities were breast carcinoma (12%), thyroid carcinoma (4%), laryngeal carcinoma, pituitary adenoma (4%); infectious comorbidities were widespread poxvirus infection (4%), Helicobacter Pylori infection resistant to 2nd line therapy (8%) and Hepatitis C virus infection recently eradicated; allergic comorbidities were allergic rhinitis (20%), asthma (16%), contact allergy (12%), atopic dermatitis (12%); immunologic comorbidities were Hashimoto thyroiditis (20%), vitiligo (8%) alopecia areata (4%), ulcerative colitis (4%), urticarial vasculitis (4%). We also divided our population in hyper-IgE and non hyper-IgE patients. 6 patients completed 2 cycles of treatment, while 14 patients completed 1 cycle of treatment and 5 patients underwent 12 weeks (1/2 cycle) of treatment to date. The majority of patients achieved consistent reduction of UAS-7 and DLQI within the first 4 weeks of treatment. A smaller percentage of patients achieved a satisfactory response after 12 weeks of treatment. Discussion: In our population Omalizumab determined a satisfactory reduction of symptoms of CSU. No serious variations regarding patients' comorbidities and concomitant medications were encountered. Real-life data are a valuable source of information about a drug's safety and efficacy profile in the short, medium and long term. This is particularly important while treating patients affected by different comorbidities and taking different medications.

23. The delicate Th17/Th17.1/Th1 balance in non-segmental vitiligo: significant
changes according to disease activity

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The delicate Th17/Th17.1/Th1 balance in non-segmental vitiligo: significant changes according to disease activity. Speeckaert R*, Mylle S*, van Geel N *Equally contributed as first author Abstract Introduction and objectives: Increasing evidence supports a role of the Th17 pathway in vitiligo with multiple reports confirming elevated circulating IL-17 levels and increased numbers of Th17 lymphocytes in non-segmental vitiligo. Nonetheless, their pathological role is less clear. Conflicting results regarding the association between IL-17 values and disease activity have been reported. Materials and methods: We conducted a thorough investigation of the T helper subsets in an extensive group of non-segmental vitiligo patients (n=77) to clarify the changes in the immune balance according to disease activity. Results were compared to healthy controls (n= 30). Results: Both in active and stable vitiligo patients we observed a link between Th17 lymphocytes and Th2, Th9 and Th22 cells while an inverse associated with Th1 cells was observed. Besides Th1 lymphocytes, only Th17.1 cells were significantly ($p = 0.015$) increased in active vitiligo patients. Th17.1 cells are therefore likely to account for a large part of the increased IL-17 levels and IL-17-producing CD4 cells reported in progressive vitiligo. In contrast, Th9, Th17 and Th22 cells were only elevated in stable disease compared to healthy controls ($p= 0.024$, $p= 0.005$, $p = 0.002$, respectively). A clearly decreased Th1/Th17 ratio was seen in stable vitiligo compared to the active counterpart ($P = 0.016$). This points to a Th1 predominance in the active process of vitiligo. Spearman's correlation revealed a positive correlation of Th17.1 with both Th1 ($rho = 0.284$, $P = 0.012$) and Th17 ($rho = 0.437$, P

24. Adult patients with atopic eczema have a high burden of psychiatric disease: a Finnish nationwide registry study

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Indroduction: Atopic dermatitis (AD) is the most common inflammatory skin disease and its incidence has been increasing over recent decades, creating a significant global health problem. AD is associated with several comorbidities. Objectives: We analyzed psychiatric comorbidities in a nationwide adult AD cohort. Materials and Method: This was a retrospective register study of all adult cases of AD diagnosed in Finnish hospitals between 1st January 1987 and 31st December 2014. Patient data was obtained from the statutory Finnish Care Register for Health Care. The study included 57690 adult patients with AD and 40363 individuals diagnosed with melanocytic nevi as controls. The prevalence of preselected comorbidities were compared between AD and control group. Conclusions: At least one psychiatric diagnosis was found in 17.2% of the AD patients and 13.1% of controls. Every psychiatric disorder studied was more common in patients with AD than in controls. We found a previously unreported finding that AD is associated with both schizophrenia (OR 1.62; 95% CI 1.41–1.88) and bipolar disorders and manic episodes (OR 1.37; 95% CI 1.21–1.55). Conclusions: Our results demonstrate that psychiatric morbidity is significant in patients with atopic dermatitis and therefore questioning the patients mental health status should be considered as a part of the standard care.

25. Early Response to upadacitinib in moderate-to-severe atopic dermatitis: Results from a Pphase 2b randomized, placebo-controlled trial

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Introduction/Objectives: Atopic dermatitis (AD) is a chronic, inflammatory, skin disease characterized by pruritic lesions. Upadacitinib (UPA), a selective JAK-1 inhibitor, is investigated for treatment of patients with AD and other inflammatory diseases. We evaluated early response to UPA treatment from the initial 16-week, double-blind portion of a phase 2b, 88-week, dose-ranging trial. Materials/Methods: Adults with moderate-to-severe AD (EASI ≥16, BSA ≥10%, IGA ≥3) not adequately controlled by topical treatment, or for whom topical treatments were not medically advisable, were randomized to once-daily monotherapy with UPA 7.5, 15, or 30 mg, or placebo (pbo). Missing data were handled by last-observation-carried-forward (continuous variables) and non-responder-imputation (categorical variables). Results: Of the 167 randomized patients; 166 received study drug (42 in each UPA dose-group; 40 in pbo). Mean percent improvement from baseline in EASI score at week 2 was 39.4%/55.9%/59.0% (p

26. Evaluation of biomarkers to predict treatment response in psoriasis: the ongoing quest

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Introduction & Objectives: Biologics are efficacious drugs for the treatment of moderate-severe psoriasis, but in clinical practice, response to these expensive drugs may vary. We currently lack biomarkers to predict these responses, although candidates have been reported in literature. Here, we evaluated these biomarkers in an independent cohort. Materials & Methods: Patients were recruited who were treated either with adalimumab or ustekinumab. Serum was collected prior to treatment initiation and disease severity was assessed before and after 6 months of treatment. Responders were defined as > ΔPASI90, non-responders were defined as

27. Intermediate ustekinumab serum concentrations correlate with clinical response in moderate-to-severe psoriasis patients

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Introduction and objectives: Ustekinumab (UST), a monoclonal antibody targeting the shared p40 subunit of IL-12/23, has been shown to be effective for the treatment of moderate-to-severe psoriasis. Similar to anti-tumour necrosis

factor biologicals however, primary and secondary non-response occurs. Whereas for adalimumab, a clear correlation between trough concentration and clinical response has been shown, this has not been observed for UST. Measuring at intermediate time points instead of at trough may be a better time point to observe a concentration-response relationship. We aimed to investigate the correlation between UST concentrations at week 4 upon injection and clinical response in psoriasis patients. Materials and methods: Forty-nine patients with severe-to-moderate psoriasis treated with UST for ≥ 16 weeks at Ghent University Hospital and affiliated Belgian dermatology clinics were included. Using a weight-based dosing regimen, 31 patients received 45 mg and 18 patients received 90 mg UST every 12 weeks. Based on absolute Psoriasis Area and Severity Index (PASI), clinical response was defined as optimal (≤1) or excellent (≤3). UST serum concentrations were measured using an in-house developed ELISA with similar performance as the JnJ assay. When UST concentrations were undetectable anti-ustekinumab antibodies (AUA) were determined using an in-house developed drug-sensitive bridging assay. Statistics were performed using the Mann-Whitney U test and Spearman rank correlation. Results: The median UST concentration at week 4 upon injection was 3.2 µg/ml (interquartile range 2.3-4.2 µg/ml). An inverse correlation was observed between UST concentrations and absolute PASI (Spearman's r = -0.312, p = 0.0291), revealing that patients with higher serum UST levels respond better to treatment. UST concentrations in patients receiving 45 mg was not statistically different from patients receiving 90 mg. In patients treated with the 45 mg dosing regimen, median UST concentrations were considerably higher in excellent responders (2.9 µg/ml vs 1.6 µg/ml in PASI≤3 vs PASI>3, respectively, p = 0.0420). Furthermore, patients with an optimal response had remarkably higher UST concentrations compared to patients with PASI>1 (4.7 µg/ml vs 2.9 µg/ml, respectively, p = 0.0154) in the 90 mg group. Only one patient had undetectable UST concentrations and was found to be positive for AUA. Conclusions: A concentration-response relationship at week 4 upon injection was observed for UST-treated severe-to-moderate psoriasis patients. Measuring UST concentrations at intermediate time points could identify underexposed patients which might benefit from dose intensification. Future research could reveal whether dried blood spot methodology would facilitate intermediate sampling in a patient-friendly manner.

28. Developing a therapeutic window for secukinumab in psoriasis: a step toward personalized therapy

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Introduction and objectives In clinical practice, psoriasis patients are treated with secukinumab according to a 'one size (dose) fits all' approach. The development of an optimal therapeutic window for secukinumab could be a first step towards a more personalized treatment and may eventually result in more accurate dosing, with potentially less overtreatment or unnecessary switching of patients. Materials and methods Serum was collected from 51 adult psoriasis patients who are treated with secukinumab 300 mg every four weeks for at least 12 weeks, for secukinumab trough level and anti-drug antibody determination and disease severity was assessed with psoriasis disease severity through measurement of Psoriasis Area and Severity Index (PASI). By receiver-operation characteristics (ROC) analysis, a cut-off value of secukinumab trough level was determined to distinguish insufficient from adequate responders. Results A negative correlation was found between secukinumab concentration and PASI at trough (r=-0.3675, p=0.0110). Secukinumab concentrations were significantly higher in excellent responders (PASI ≤ 3) compared to moderate responders (PASI > 3) (p=0.0082). Confounding variables which were negatively correlated with STL levels and/or PASI were smoking, waist circumference, secukinumab treatment duration and former treatment with adalimumab and/or ustekinumab. With an area under the curve (AUC) of 73.59% (95% CI 0.5883 – 0.8834 and p=0.00086) we concluded that determining the secukinumab trough level is a valuable test to distinguish excellent clinical response (PASI ≤ 3) from moderate response (PASI > 3). A secukinumab trough level of 33.15 µg/mL corresponded with the most favorable trade-off value between sensitivity (75 %) and specificity (70.97%). With a secukinumab concentration above 33.15 µg/mL, patients have a 7.33 times higher chance to be excellent responders (OR=7.333, 95% CI 2.008–24.02, p=0.0048). Due to low sample size, a concentration-effect curve could not yet indicate an upper limit to define the therapeutic window. Conclusion We report for the first time a lower therapeutic threshold concentration of 33.15 µg/mL for secukinumab at serum trough in a psoriasis cohort. Patients with secukinumab trough concentrations below 33.15 µg/ml may be potentially undertreated. These results state the correlation between serum secukinumab concentration and treatment response.

29. Discontinuing etanercept in patients with psoriasis in remission

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Introduction & Objectives: This study investigate the disease course in those patients with diffuse PsO who asked for drug discontinuation after achieving a complete and persistent clinical remission. Materials & Methods: We assessed 108 patients with PsO in treatment with etanercept in complete and persistent clinical remission. 53 of the 108 patients make explicit request to interrupt the therapy. Such patients in the experimental group ("stoppers") were compared with 55 patients who continued therapy with etanercept continuously ("non stoppers"). The proportion of patients who relapsed, the mean time to relapse and the PASI score at that time were estimated in patients who discontinued versus those who continued etanercept. Time to relapse was estimated in the stoppers group using the Kaplan-Meier method. Cox proportional hazard models were assessed to identify factors related to relapse. Results: Of the 108 patients with PsO in complete clinical remission, relapse was observed in 38 patients; 33 (62.26%) in the stoppers group and 5 (9.09%) in the non-stoppers group. In the stoppers group the median PASI score at the re-uptake was 8 (4-10). The median time-to-relapse was 184 days in the "stoppers" group while it was not reached by "non-stoppers". Among sex, age, onset age, BMI, hypertension, diabetes, dyslipidemia and severity as PASI at the beginning of therapy with etanercept no one was statistically significant as possible predictive factors of relapse. Conclusions:These data show that discontinuation of etanercept may be associated with a prolonged clinical benefit for a sizeable proportion of patients in stable clinical remission.

30. Risk of periodontal disease in patients with chronic plaque psoriasis

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Introduction Psoriasis is a common, chronic, inflammatory, multisystem disease affecting approximately 2% of population. It has been associated with certain diseases and there is a strong link between metabolic syndrome and psoriasis. Chronic periodontitis is an infectious disease resulting in inflammation within the supporting tissues of the teeth, progressive attachment loss, and bone resorption and clinically characterized by pocket formation and/or gingival recession. Psoriasis and chronic periodontitis share common risk factors and co-morbidities. Objective The aim of our study was to determine how frequently chronic periodontitis is associated with patients with psoriasis compared to systemic healthy subjects and if its presence is associated to severity of psoriatic lesions. Methods Baseline demographic data including sex, age, smoking habits, family history of psoriasis or periodontal disease was recorded in 55 psoriasis subjects and 55 healthy subjects. Information on comorbidities and pharmacological treatment, daily tooth brushing, the presence of gingival bleeding, location of skin lesions, weight and height were also evaluated. The periodontal clinical parameters probing depth, periodontal attachment level, plaque index and presence or absence of radiographic bone loss were recorded. The severity of psoriasis was assessed by Psoriasis Area and Severity Index. A complete blood test was asked for all subjects included in the study. Results During the study enrolment period 55 patients with psoriasis and 55 age- and gender-matched controls were included in this study. Probing depth and periodontal attachment level showed significant higher values in psoriasis group compared to healthy subjects. Conclusions We found evidence of a psoriasis-associated increased risk of periodontitis. Thus, dermatologists should be aware of this comorbidity because these patients should be closely followed-up by a dentist for the adequate and early treatment of periodontitis. Periodontitis may be associated with psoriasis but further studies are needed to elucidate their relationship.

31. Apremilast efficacy and safety in a psoriatic arthritis patient affected by HIV and HBV virus infections

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Introduction & Objectives: Treatment of psoriasis and psoriatic arthritis in patients with concomitant chronic, severe infections represent a challenge, due to contraindication to conventional immunomodulating systemic drugs and biologics, such as anti-TNF alpha, anti-IL 12/23 and anti-IL 17 agents. Recently apremilast, a selective inhibitor of phosphodiesterase E4, has been authorized and may represent a safe and effective therapeutic option to treat HIV infected population with psoriatic arthritis. We report the case of a 41-year-old patient affected by arthropathic psoriasis, HBV-related chronic hepatitis and concomitant HIV infection, treated with Apremilast. Materials and Methods: This study is a case report and literature review. Results: After 24 weeks of therapy patient achieved a 90% improvement from baseline PASI score and a considerably DLQI score reduction. With regard to PsA, disease activity

was substantially reduced (from a DAS28 of 3.46 to a DAS28 of 1.74) with significant improvement in his quality of life. No severe adverse events or side effects were observed or reported during the course of treatment. In relation to HIV infection, monitoring of viral load by quantitative PCR and of the lymphocyte count by cytofluorimetric examination showed no significant alterations. Conclusions: Our experience suggests as Apremilast could represent the first choice of therapy in patients with psoriasis and concomitant severe infections.

32. Apremilast, psoriasis and chronic liver disease

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Introduction Several recent reports have shown a relationship between psoriasis and chronic liver disease utilising non-invasive imaging. While the exact aetiology of this relationship remains uncertain, it has been postulated that inflammatory cytokines such as resistin, tumour necrosis factor alpha (TNF-α), IL-6 and IL1-β play a mechanistic role in the development of insulin resistance and fatty liver as well as psoriasis. These connections imply a possible linked pathogenesis further supported by similarities between skin and liver inflammation. Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of disease states ranging from isolated fatty liver to non-alcoholic steatohepatitis (NASH) with increasing levels of fibrosis and ultimately cirrhosis. While NAFLD can be identified with ultrasound alone, liver biopsy is necessary to definitively distinguish isolated steatosis from NASH and other liver disorders. Methods 126 patients between the ages of 18 and 80 years with a diagnosis of psoriasis in treatment with apremilast were considered for enrollment in the study over a 6-18 month period. Ultrasound studies were done per standard protocol. Blood was collected for evaluation of liver associated enzymes, HgbA1C and lipid studies. Iron studies, alpha-1 anti-trypsin, a chronic viral hepatitis panel, anti-nuclear antibody, anti-smooth muscle antibody and ceruloplasmin were also collected from these participants. Results 75 patients were diagnosed of chronic liver disease utilising non-invasive imaging: 40 NAFLD, 5 NASH (a biopsy was performed on 14 patients), 21 chronic liver disease (viral hepatitis or unknown origen) and 9 cirrhosis. 25 patients were followed by the Division of Digestive at Hospital Marqués de Valdecilla, Santander. 57 patients were selected in which no change in medication or alcohol consumption had been introduced. In the same way they did not suffer modifications in their weight. FIB-4 was used as a predictor of fibrosis due to its simplicity. The results were: 29 patients in tto with apremilast improved the value, 11 worsened and 17 remained unchanged. Among patients who worsened several were on combined treatment with methotrexate and consumed alcohol. In 3 patients the values of FIB-4 were in discordance with an objective improvement of ultrasound studies. Conclusion Although deeper studies with a control population and a longer time interval are required, this preliminary study suggests that apremilast could offer clinical benefits in liver disease attenuating pro-inflammatory TNFα-mediated liver injury, likely through downregulation of transcription factor NFκB. Apremilast also interferes with the production of inducible nitric oxide synthase which is involved in the development of liver fibrosis. Further PDE4 is a cAMP-specific phosphodiesterase expressed in several brain regions that regulates the reinforcing effects of drugs of abuse as alcohol.

33. A case of Psoriasis and cutaneous T-cell lymphoma: Emphasizing the need for biopsy confirmation before starting biologics

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Introduction It has been reported that patients with psoriasis are at increased risk for developing lymphoma including cutaneous T-cell lymphomas (CTCL). It is most possibly related to the chronic lymphocyte stimulation that occurs during psoriasis that eventually leads to a dominant clone and the evolution to CTCL. Case report We describe a case of a 54-year-oldman, smoker and cannabis consumer, with a 50 years history of psoriasis, and comorbidities such as depression, hepatitis c, b and fatty liver. He presented with erythroderma in the course of psoriasis, with contraindications to other classic psoriasis therapies. He had inguinal lymphadenopathy. We start therapy with apremilast at a dose of 30 mg bid and phototherapy .Althought there was improvement in Psoriasis Area and Severity Index score, the patient abandoned the medication because of his personality disorder. Acitretin 25 mg was started (he had been treated like this in the past) ; however, his symptoms worsened to include progressive skin involvement and fever, which led to hospitalization. Physical exam revealed diffuse erythematous desquamative plaques from head to toe. He received oral prednisone (50mg/d). The blood count showed normal red cell count and a slight leukocytosis. Peripheral blood film for Sézary cells was negative but 0.18% cells was CD28+, CD25+, CD45RO+.Three punch biopsies

were performed, two of which revealed parakeratosis with underlying pallid keratinocytes, subjacent neutrophils forming conical pustules, and a perivascular lymphocytic infiltrate. These findings were most suggestive of psoriasis. The patient's clinical features and skin pathology were compatible with erythrodermic psoriasis. The third biopsy only showed a poor epidermotropic infiltrate of medium-sized lymphocytes. An excisional biopsy of the inguinal lymph node showed dermatopathic and reactive lymphadenitis. Subsequent bone marrow biopsy revealed morphologic evidence of an underlying lymphoproliferative disorder (CD3, CD4, CD7+). Positron emission tomography (PET)-CT identified metabolic lesions involving superficial soft tissues underarm. The patient was then switched to bexarotene (150mg/d) and concurrent total skin electron beam therapy. Conclusions Psoriasis can present with erythroderma and Monoclonal hematologic disorders have been increasingly diagnosed in the last decade . CTCL is the most common lymphoma affecting the skin. Affected skin areas often resemble eczematous or psoriasiform dermatitis clinically. Repeated biopsies are frequently needed to confirm the diagnosis even in cases of clinically suspected CTCL. It provides evidence for the importance histologic verification of the diagnosis of Erythrodermic psoriasis before initiation of systemic treatment that may detrimentally affect the course of CTCL. In our case, apremilast was a right choice before lymphoma treatment.

34. Treating a Multidrug-Resistant Psoriatic with Combination Adalimumab, methotrexate, prednisone and Apremilast Therapy

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Introduction Nowadays, even though several biologic therapies are available to treat psoriasis, multidrug-resistant disease continues to be a therapeutic challenge. Combination therapy has therefore become increasingly important. In this context, apremilast, according to its safety profile, could easily be combined with biologics in patients with comorbidities and/or recalcitrant multidrug-resistant psoriasis. Case report Our goal is to share experience from our institution in the observation of a 28 year female patient with severe chronic plaque psoriasis that was unresponsive to all anti-tumor necrosis factor-α treatment, ustekinumab, secukinumab, ixekizumab and apremilast. Our patient (Psoriasis Area Severity Index score 50), commenced adalimumab weekly, Prednisona 50 mg/d and metotrexato 20mg/w.The patient showed good response but althought she lost infiltration and peeling she remained erythrodermic. Then we associate apremilast . The patient tolerated the treatment well and achieved excellent results, with most of the plaques clearing up. Apremilast allowed to remove prednisone and decrease the dose of methotrexate in 1 month. The patient experienced continued success with Combination therapy with lesions limited to only occasional flares.

35. Treatment of palmoplantar psoriasis with acitretin versus methotrexate versus topical clobetasol propionate 0.05%: a case series

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Objectives: to compare the efficacy and safety of acitretin, methotrexate and topical clobetasol propionate ointment 0.05% in patients with palmoplantar psoriasis in real life. Materials and Methods: a cases series retrospective study of 76 patients with palmoplantar psoriasis in therapy with acitretin (n=31) at dose of 10 mg/day; methotrexate (n=11) at dose of 12.5 mg/week; topical clobetasol propionate 0,05% ointment applied once/day (n=34). Disease severity was assessed by Palmoplantar Psoriasis Physician Global Assessment (PPPGA) at baseline, week 8 and 24. Safety was assessed by reporting every adverse events occurred in the 24 weeks of observation. The primary outcome was the proportion of patients achieving PPPGA 0 (i.e. clear) at week 24. Results: the primary outcome was achieved by 82% of patients treated with acitretin versus 60% of those with methotrexate versus 21% of clobetasol propionate 0.05%

36. A case of generalized pustular psoriasis and arthritis treated with ixekizumab

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Introduction & Objectives: Generalized pustular psoriasis (GPP) is a severe variant of pustular psoriasis, in which acute generalized erythema and scaling develop with a rapid spread of multiple sterile pustules. GPP is often associated with systemic inflammation and general malaise. It can be persistent or recurrent, and it can be complicated by hypoalbuminemia, hypoparathyroidism and arthritis. Fatal outcomes have been observed. The aim of this case was to evaluate the efficacy and safety profile of ixekizumab in GPP. Materials & Methods: We describe the case of a 32-year-old Caucasian female who had a history of psoriasis from the age of 21 years, and who was admitted to our department

with a generalized pustular rash, fever and general malaise. The physical examination found multiple pustules coalescing into very painful purulent lakes on her trunk and limbs and legs. She had previously been treated in other dermatology department with corticosteroids and cyclosporine, but with little effect. Biological treatment with adalimumab was initiated but after six months a significant response was not observed. We decide to switch the patient to infliximab and after two months of treatment, we found an almost immediate improvement. Then, 8 weeks after of infliximab treatment she refers pain at the joint and swelling, and again after 10 weeks of treatment, the rash appears again as generalized pustular psoriasis. We decide to switch the patient to ixekizumab after one month of wash out. Results: The patient was treated with ixekizumab 160 mg s.c. at the baseline and then 80 mg s.c. every 2 weeks. We observed a very good improvement of cutaneous symptoms just after two injections of ixekizumab and good result in terms of pain and swelling at the joints. Conclusions: In our experience, this is the first case of GPP treated with ixekizumab, the drug was safe, well tolerated and was efficacy on cutaneous and joint symptoms.

37. Adalimumab in plaque psoriasis. Real world experience in the era of the multitarget biological treatments

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Introduction Adalimumab is a first-in-class humanized antibody directed against TNF-alfa. Currently there are many directed biological therapies used in psoriasis. Nevertheless, adalimumab endures as a safe and effective treatment in this clinical setting. Objectives The objective of this study is assess effectivity of adalimumab in actual clinical practice in the era of multiple biological therapies. Materials and Method A unicentric retrospective observational study was conducted. Patients with psoriasis treated with adalimumab who had been given the medication between January 2017 and June 2018 were selected from pharmaceutical register of our hospital. Medical records were retrieved and epidemiological data of patients was assessed. Baseline PASI and PASI-75 and -90 achievements were scored at weeks 16, 24, 52, 156 and 260 Results 39 patients with psoriasis were treated with adalimumab between 2017 and 2018 (26 men and 13 women). Treatment was started between 2007 and 2018. Average age at the moment of the treatment was 46,7 years. Average body mass index was 27,5. Baseline PASI value was 12. Median follow up was 200 weeks. PASI-75 was achieved by 78% patients at week 16 and by 96% and 92% at weeks 52 and 156 respectively. PASI-90 was achieved by 62% patients at week 16 and by 75 and 73% at weeks 52 and 156 respectively. Treatment with adalimumab was suspended in 6 patients (15,8%) throughout the follow-up. The main reasons for discontinuation of adalimumab were lack of efficacy or loss of efficacy. Any patient discontinued adalimumab due to adverse events. 26 patients (66,7%) were followed for more than 3 years and we observed a adalimumab-persistence rate of 92,3% in these patients. Conclusions Adalimumab is a safe and effective treatment of psoriasis, with excellent rates of persistence at 3 years.

38. Survival of Adalimumab in plaque psoriasis: Experience of clinical practice in a tertiary hospital in Valencia, Spain

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INTRODUCTION Adalimumab has been shown to be an effective and safe drug in the treatment of plaque and joint psoriasis. Clinical trial data are always made on selected populations, so there is a bias when we extrapolate them to our patients on a day-to-day basis. For this reason, it is essential to analyse the data available in routine clinical practice. SUBJECTS AND METHODS Retrospective study carried out at the Dermatology Service of the La Fe University and Polytechnic Hospital in Valencia, Spain. We included all patients who had received at least one dose of Adalimumab, with indication of plaque psoriasis, during the period January 2009 to December 2017, with a minimum follow-up in routine clinical practice of three months. The main objective of the study was survival analysis using the Kaplan Meier method. Secondarily, we analyze the distribution by sex and age, together with the evolution of the absolute PASI over time. RESULTS A total of 88 patients were included, 45 men and 43 women, of whom 38 are still on current treatment (43%). In 59 patients, the drug was used as a first line of treatment (67%), with second, third and fourth lines of treatment in 27 (30%), 7 (8%) and 1 (1%) patients respectively. In all cases the drug was used with the dosage of technical data sheet, except in six patients where the drug was de-intensified to 40 mg every 3 weeks, and two cases with intensification to 40 mg/week. The mean treatment time was 21 months (SD 29.33) with a maximum survival of 101 months. According to our data, the estimated survival during the first, second and third year of treatment after its initiation was 71.40%, 49.50% and 37.40% respectively. The graphs of the absolute PASIs recorded as a function of time will be displayed. CONCLUSION Our survival data, including 101 months of treatment, allow us to conclude that Adalimumab is a drug that allows adequate and lasting control of psoriasis.

39. Sustained response to adalimumab over multiple years in patients xith plaque psoriasis: Analyses from the British Association of Dermatologists' Biological

Interventions Register (BADBIR)
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Introduction & Objectives: Psoriasis is a chronic disease requiring lifelong treatment. This study analyzed BADBIR registry data to evaluate response to ADA over multiple yrs. Materials and Methods: We assessed response in 2 cohorts, ADA and conventional therapy, every 6 months through yr 3 and then yearly thereafter (observed data through September 2017) in pts with plaque psoriasis. A diagnosis of severe psoriasis unresponsive to conventional therapy was required to qualify for biologic therapy. For inclusion in the BADBIR registry, pts were required to have initiated or switched to a biologic or conventional therapy within the previous 6 months; pts initiating their first conventional therapy had to have a Psoriasis Area and Severity Index (PASI) ≥10 and Dermatology Life Quality Index (DLQI) >10. Differences between treatment cohorts were determined for proportions of pts achieving a ≥75%, ≥90%, and 100% improvement in PASI (PASI75, PASI90, and PASI100, respectively), Physician Global Assessment (PGA) score of 0–1, and DLQI of 0–1; P values for differences were based on chi-square test. Results: A total of 4924 pts in the ADA cohort (baseline mean age, 45 yrs; 59% men; 26% with psoriatic arthritis) and 4877 in the conventional therapy cohort (baseline mean age 44 yrs; 56% men; 9% with psoriatic arthritis) were included. At baseline, mean ± SD PASI was 12.8±8.9 and 14.7±8.0 for ADA and conventional therapy cohorts, respectively. The proportions of pts with PASI75, PASI90, and PASI100 responses were significantly greater with ADA vs conventional therapy at all assessed time points over a 7-yr period

40. Efficacy and safety of risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis: Results from the phase 3 IMMvent trial

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Introduction/Objectives: To investigate the efficacy/safety of RZB vs. originator (ADA) in patients (pts) with moderate-to-severe plaque psoriasis. Materials/Methods:In the phase 3 IMMvent(N=605),trial, pts were stratified by weight, prior TNFi-exposure and randomized 1:1 to receive 150mg RZB(N=301, week [wk] 0, 4, 16, and 28) or ADA(N=304, 80mg at wk-0, 40mg every other week [eow] from wk-1). Wk-16 ADA-treated pts achieving PASI 90 response continued on eow ADA

41. Risankizumab efficacy/safety in moderate-to-severe plaque psoriasis: 16-week results from IMMhance

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Background/Objectives: Risankizumab is a potent humanized IgG1 monoclonal antibody that inhibits IL-23 by specifically binding its p19 subunit. Here, we report efficacy and safety results of risankizumab from initial 16-week (wk) placebo (PBO)-controlled period of IMMhance trial in patients (pts) with moderate-to-severe chronic plaque psoriasis (PsO). Methods: IMMhance (NCT02672852) is a phase 3 multicenter, randomized, double-blind, PBO-controlled trial, evaluating the efficacy and safety of risankizumab versus PBO in pts with moderate-to-severe chronic plaque PsO. The initial 16-wk PBO-controlled period (507 pts, stratified by weight and prior TNFi-exposure, randomized 4:1 to receive either risankizumab [150 mg at wks 0 and 4] or PBO) was followed by randomized withdrawal and subsequent re-treatment with risankizumab. Co-primary endpoints were PASI 90 and sPGA 0/1 responses at wk 16; missing data were imputed as non-responders. Results: At baseline, the mean age and weight were 49.2 years and

92.0 kg, respectively; 70.2% of pts were male. A history of diagnosed or suspected psoriatic arthritis was reported in 34.7% of pts and prior TNFi therapy was reported in 36.5% of pts. Mean baseline PASI and BSA were 20.2 and 26.1%, respectively. At wk 16, all primary and ranked secondary endpoints were met

42. Inflammatory pseudotumor of the skin

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CLINICAL CASE A 70-year-old man presented with a 6-month history of an asymptomatic but growing nodule on his left thigh; on physical examination the nodule was 4 cm in diameter, well circumscribed and firm. The primary clinical differential diagnosis considered included mesenchymal neoplasia, cutaneous lymphoma, cystic formation, giant dermatofibroma. Ultrasound investigation showed a mixed hyperechoic-hypoechoic mass and there was no vascularization on ecodoppler. We elected to perform skin biopsy for making the diagnosis and the pathology report described a proliferation of fibroblastic-myofibroblastic cells with a mixed inflammatory infiltrate. Immunohistochemistry was negative for ALK and showed positivity for vimentin, XIIIa, beta cytoplasmic catenin and cd10. These histologic findings led to a diagnosis of inflammatory pseudotumor of the skin. Treatment was surgical excision with complete removal of the lesion. By 3 months postoperatively, no recurrence was evident. DISCUSSION The term inflammatory pseudotumour was originally used for any lesion which simulated a neoplastic condition. In more recent times, the term has been employed in a more restrictive sense for lesions of different biological potential characterized by the proliferation of fibroblasts and myofibroblasts with a heavy inflammatory infiltrate of mixed composition. Inflammatory pseudotumour occurs in various organs and among them, the lung is the most frequently affected followed by the liver, lymph node and spleen. Primary cutaneous involvement is very rare and less than 20 cases of inflammatory pseudotumour of the skin have been reported in the literature. The clinical presentation is not specific and this lesion varies in size and shape; the patients generally present with a mass without specific symptoms. No local recurrence, metastasis, malignant transformation or lymph node involvement were observed in any of the described cutaneous cases. The treatment of choice is surgical excision with clinical surveillance.

43. Causes of death in kidney transplant recipients: a multicenter cohort study

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Introduction Causes of death in kidney transplant recipients have been investigated, but with conflicting results. Materials and methods. Multicenter cohort study including 6789 patients, with a median 9-year follow-up. Cumulative incidence, multivariate analysis with competitive risk model, and standardized mortality ratio (SMR) in comparison to non-immunosuppressed age and sex matched Italian population, were computed. ICD X classification of diseases and Stata 10 statistical software (Statacorp LP TX USA) were used. Results. Overall mortality was significantly increased (n=814; SMR 2.7). The main causes of death were cardiovascular diseases (SMR 5.6), severe infections (SMR 15.9) and cancers (SMR 1.1, 95% CI 0.8-1.3). Female patients presented an excess mortality, if compared to non-immunosuppressed females in general population, that was higher than in males, for all causes (SMR 7.9 vs 4.4), for cardiovascular diseases (SMR 26.0 vs.7.6), acute myocardial infarction (SMR 39.6 vs. 8.6), ictus cerebri (SMR 31.3 vs 9.4) and pneumonitis (SMR 26.7 vs 0.8). Cancer- related mortality was significantly more elevate in patients younger than 40, and lower than expected in patients older than 60. The main cancer- related causes of death were post-transplant lymphoma (n= 41, SMR =5.4), cancer of the native kidney, ovary and bladder cancers, and squamous cell carcinoma. No excess mortality was detected for cancers commonly observed in the general population as cancers of the lung, colon, and female breast. An excess mortality due to chronic liver diseases and suicide was observed. Conclusions. Female patients undergoing kidney transplantation lost their survival advantage if compared to men, especially for cardiovascular disease. Cardiovascular diseases and infections were the more common causes of death in the study population. Cancers had a limited impact on mortality, except for post-transplant lymphomas, squamous cell carcinoma of the skin, and rare cancers.

44. The first case of Natalizumab-induced Subacute Cutaneous-Lupus Erythematosus and review of biologic-induced reactions

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Background:
Biologic-induced subacute cutaneous lupus erythematosus is rarely reported in the literature.[1] With the time delays incurred in processing serological tests, recognition of dermatological signs may be critical to diagnosing rheumatological conditions and the complications incurred in therapies prescribed. We present the first reported case of Natalizumab-induced SCLE and summarise 23 reported cases of SCLE induced by 13 different biologics.
Case Report:
A 51 year old gentleman presented with a 6 week history of a rash following his second Natalizumab infusion- a second line therapy given monthly for multiple sclerosis. Over his arms, trunk and legs he had well-demarcated erythematous annular lesions forming confluent patches with sparing of surrounding skin, there was no blistering or lymphadenopathy. He experienced an isolated febrile episode of 39° and was pancytopenic (Neutrophils $1.9x10^9$/L, lymphocytes $0.28 x10^9$/L, Platelets $85 x10^9$/L). The differential included drug-mediated immune reaction, erythema multiforme (EM) or cutaneous manifestation of malignancy.
Common viral aetiologies for EM were excluded and thoracic-abdominal-pelvic CT scan was unremarkable. Skin biopsy showed a non-conclusive vacuolar interface dermatitis. With topical and oral corticosteroids, his rash improved and was labelled as EM. During follow up, re-review with immunology results (Anti-dsDNA negative, Anti-Ro positive and ANA titre 1:640) prompted a revised diagnosis of subacute cutaneous lupus erythematosus (SCLE) with systemic involvement.
Discussion:
On comprehensive review of English and Non-English literature we identified 23 cases of biologic-induced SCLE and outline the common features. With increasing reporting of SCLE triggered by biological therapies clinicians should be aware of the cutaneous hallmarks of the condition. Recognition of the lesions may avoid unnecessary investigations, hasten appropriate treatment and alert to future diagnoses; with 25% of patients with SCLE found to progress to systemic lupus erythematosus within 3 years.[2]
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