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Autoinflammatory diseases in children and adults

SP0080 RECURRENT EPISODES OF FEVER AND ARTHRITIS IN ADULT PATIENT

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Background: Familial Mediterranean Fever (FMF) is a relatively rare condition that belongs to the more recent group of autoinflammatory diseases (AIDs)[1]. It primarily affects patients with Mediterranean or Middle Eastern origins and its clinical setting includes short, recurrent episodes of fever, serositis, skin rash and a high risk of amyloidosis[2]. FMF is an autosomal recessive transmitted disease and several mutations of the Mediterranean fever gene (*MEFV*) on chromosome 16 have been identified[3]. Patients respond well to colchicine therapy or if necessary, biological therapy with anti-IL 1, IL6 or anti-TNF could be initiated[4]. Establishing the right diagnosis might raise difficulties for rheumatologists who are not fully accustomed to this condition.
Objectives: To evaluate the clinical course, specific features and treatment difficulties of a male patient diagnosed with FMF in adulthood, based on the description of a case report.
Methods: Case-description using patient's medical records and investigations.
Results: This is the case report of a 37-year old male patient currently admitted for right knee arthritis and high grade fever (39.1℃). His medical history dates back at age 16 when he presented in the Pediatric Department with recurrent episodes of prolonged fever (up to 40℃), diffuse abdominal pain together with myalgia, arthralgia accompanied by increased acute phase reactants; after various sources of infection and hematological malignancies were excluded, physicians noted positive low titer ANA (1/20) but normal complement fractions, absent lupus (LE) cells. Further medical investigations showed a negative rheumatoid factor, ACPA, negative antibodies' panel (dsDNA, Sm, Ro, U1-RNP) and absent cryoglobulins but a positive HLA B27. No signs of sacroiliitis were detected on the x-ray. Patients' repeated complaints of knee or ankle arthritis together with later finding of positive anti-Salmonella and anti-Shigella antibodies leaded to establishing the diagnosis of reactive arthritis. Due to symptoms' persistence and reoccurrence under non-steroidal anti-inflammatory drugs, he was prescribed high dose corticosteroids and sulfasalazine. At age 20 the patient presented with recurrent arthritis of the knees and ankles, fever (38.5℃) and abdominal pain with markedly elevated inflammatory markers. The abdominal ultrasound highlighted a splenomegaly and peritonitis. Colchicine treatment was initiated and his favorable response led to MEFV genetic testing that revealed a mutation of the 10.1 exon, thus confirming the diagnosis of FMF by fulfilling two major criteria of the Tel-Hashomer diagnostic set. Subsequently, he performed a gingival biopsy that excluded the presence of amyloid deposits. Patient's partial response to colchicine with repeated incomplete attacks of FMF and persistent inflammatory syndrome led to the initiation of biological therapy with Etanercept along with Sulfasalazine and glucocorticoids, due to temporary unavailability of an anti-IL1 agent. Patient's delay in diagnosis and longstanding corticosteroid therapy led to major articular consequences (bilateral aseptic osteonecrosis of the femoral head with requiring hip arthroplasty).
Conclusions: This case presentation depicts the hardships of setting the right diagnosis in a case of late onset FMF due to unusual geographical setting, absence of suggestive family history and heterogeneous clinical presentation together with possibilities in therapeutic approach if patients are non or partially responsive to traditional therapies. Furthermore it points out possible drug side effects and comorbidities that require the same quality medical care as the main rheumatic disease.
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Immunogenicity of biologics; myth or reality?

SP0081 THE T CELL RESPONSE TO THERAPEUTIC ANTIBODIES

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Therapeutic antibodies (TMabs) are part of the best successful therapeutic products of the last decades. They are currently used to treat many inflammatory diseases such as rheumatoid arthritis (RA) and bowel diseases and represent worldwide a market of several billions of dollars. However they have the major drawback to be potentially immunogenic and therefore might elicit anti-drug antibodies (ADA). ADA could dramatically reduce the efficacy of the drugs or might provoke allergic reactions. Because generally self-proteins are less immunogenic than foreign proteins, the sequence of therapeutic antibodies has been humanized. However humanization even at the highest level does not fully guarantee the lack of immune responses demonstrating the important need to know more about ADA response. Because T cells are known to initiate the ADA response, we are currently investigating the T cell response to immunogenic therapeutic antibodies. With the perspective of immunogenicity prediction, we quantified the number of very rare T cells specific for therapeutic antibodies in the blood of normal donors and found a good concordance between the number of T cells specific to them and their respective clinical immunogenicity level. We then identified the CD4 T cell epitopes of four immunogenic TMabs with different levels of humanization, namely the chimeric antibodies Infliximab (Ifx) and Rituximab (Rtx), the humanized antibody Natalizumab (Ntz) and the fully human Adalimumab (Adm). CD4 T lymphocytes were expanded by several weekly rounds of stimulation with autologous dendritic cells loaded with each of the investigated antibodies and the T cell specificity was assessed by IFNg ELISPOT using overlapping peptides encompassing the whole sequence of their variable parts. Nine epitopes were identified in the VL and VH chains of Rituximab and Infliximab. They overlap CDR or FR regions of both chimeric antibodies and some of them are shared by multiple donors. As inferred from binding experiments, T cell epitopes often exhibited a good affinity for HLA-DR molecules found in the responding donors. Nine CD4 T cell epitopes were found in the VH and VL parts of the humanized therapeutic antibody Natalizumab while the fully human antibody Adalimumab hosted 10 T cell epitopes. As a result, the number of T cell epitopes is very similar across the different therapeutic antibodies but their location is highly variable from one antibody to another one. Finally to assess the clinical relevance of the identified T cell epitopes, we evaluated the ability of Ifx and Rtx T cell epitopes to stimulate T cells of patients having developed ADA. Two third of the T cell epitopes identified from the healthy donors stimulated PBMCs from ADA+ patients and promoted the secretion of a diversity of cytokines. These data emphasize the predictive value of evaluating the T cell repertoire of healthy donors to anticipate and prevent immunogenicity of therapeutic antibodies. Together our data provide new insights on the origin of immunogenicity of chimeric, humanized and human therapeutic antibodies.
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SP0082 IMMUNOGENICITY OF BIOLOGICS IN INFLAMMATORY BOWEL DISEASES

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Anti-tumor necrosis factor-alpha and anti-integrin monoclonal antibodies show great benefits for inducing and maintaining remission, healing the mucosa and restoring the quality of life of patients with inflammatory bowel diseases. The therapeutic potential of these intrinsically powerful biologicals is tempered by a high variability in clinical response. Whereas primary non-response is defined as the lack of clinical response to treatment, assessed 8–12 weeks after initiation, secondary loss of response is defined as loss of clinical benefit after initially responding which can be attributed to disease-related or drug-related factors. Assays have been developed to determine the concentration of the therapeutic antibody in serum of the treated patient. The trough concentration is the concentration just before the next administration and for practical reasons therapeutic drug monitoring is mainly based on measurement of these trough concentrations. Several studies have reported correlations between through concentration of infliximab, adalimumab, golimumab, vedolizumab and clinical outcome. Optimal therapeutic windows have been defined for both infliximab and adalimumab. A panel of prospective studies in which dosage regimens are adapted in order to achieve target trough infliximab concentrations that correlate with beneficial therapeutic outcomes have been initiated.
Immunogenicity is the capability of biologicals to elicit an unwanted immune response that results in the formation of anti-drug antibodies. Anti-drug antibodies can be non-neutralizing or neutralizing. Non-neutralizing antibodies do not impair the drug-target interaction but may increase clearance of the drug resulting in lower serum concentrations. Neutralizing anti-drug antibodies compete with the target for the antigen-binding site and modulate directly the activity of the drug in addition to the enhanced clearance of the drug. A number of anti-drug antibody assays to quantify the immunogenicity of biologicals have been developed. Most of the assays quantify the total amount of anti-drug antibodies but comparing anti-drug antibody concentrations between different assays is hampered by the

use of different calibrators and by the fact that drug tolerance differs among assays ranging from extreme drug sensitive over various forms of drug tolerant to drug resistant anti-drug antibody asssays. The clinical relevance of the different type of anti-drug antibody assays remains to be proven.
Combining therapeutic drug concentrations and anti-drug antibody concentrations with relevant patient, disease and drug information will lead to optimal dosing of patients aiming at optimal clinical, biochemical and endoscopic outcomes.
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SP0083 AS A RHEUMATOLOGIST, DOES IT HAVE ANY CONSEQUENCE IN MY DAILY PRACTICE?

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It is nearly inevitable that when we administer foreign (even humanised) proteins intravenously or subcutaneously to a person, that said person will develop antibodies to that (foreign) protein. This happens to most of our patients when we administer biologicals; depending on the sensitivity of our methods, we can measure these anti-bodies easily or not at all. These antibodies start becoming a problem when they are actually binding the administered biological, thus making the active drug less available for its targeted function. We can evaluate this by measuring the actual drug-level, so called trough level. Numerous reports have been published, showing that there is indeed a negative correlation between e.g. anti-tumor necrosis factor (TNF) drug antibodies and the efficacy of anti TNF in the treatment of RA. It has also been shown that adding methotrexate (MTX) to the anti-TNF treatment improves its efficacy and reduces the level of anti-drug antibodies. Probably only 10 mg MTX weekly would be enough to obtain this effect.
So what do I do as a clinician when I observe that a patient, who originally did very well, loses response to her biological? Do I measure possible anti-drug antibodies? No, the consequences are zero: When the patient is not responding to the given drug anymore, I need to adapt the treatment; the drug she is using is not effective anymore, so we should change. Would the presence of anti-drug antibodies influence my decision? No, there is no cross-reactivity to other biologicals (even from the same class of action), except to its biosimilar (underscoring that it is a real biosimilar!). In case there is doubt whether a patient is actually using the biological we could better measure the drug-trough level; but –in my practice- this question seldom arises in patients with active arthritis, being treated with a biological.
Measuring drug-trough levels is a completely other item, and perhaps more relevant. Biologicals are in general given in a standard fixed dosage, while there are clear differences in patients characteristics, that could influence bioavailability of the biological. In addition when the disease is more active, it could be that more biological is needed to temper the inflammation compared to low disease activity, where perhaps a lower dosage would be more than effective. To guide physician and patient in personalizing and optimizing treatment with biologicals measuring drug-trough levels might be helpful. Different studies have been performed trying to use through level of the drug in adapting the dosage, and even in predicting possibility to stop the drug treatment. This area is still being evaluated and it is too early to make firm statements, but with a look at cost-effectiveness this will certainly become relevant.
Coming back to the original question: do I use anti-drug antibodies in my daily practice to guide treatment: no, it doesn't influence my decisions. Will I use in the future drug trough levels to guide treatment decisions: this could well be, but it is too early to make a final decision yet.
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Which target / outcome is more relevant in the management of SLE?

SP0084 BIOLOGICAL TARGETS IN SLE

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SLE is a prototypical condition characterized by the complete subversion of immunological tolerance and the generation of autoantibodies directed against a wide array of ubiquitous and tissue-specific antigens. This is possible because the joint dysregulation of the innate and adaptive arms of the immune system; which results from multiple gene polymorphisms, each contributing marginally, distinct epigenetic regulation, alteration of the threshold of activation for T and B cells, enhanced responses of antigen-presenting cells resulting from the altered disposal of apoptotic cells, as well as dysregulation of cytokine circuitries including regulatory networks.
Pathogenic mechanisms resulting in clinically overt SLE very likely are heterogeneous among individuals. Thus, the identification of biological targets in SLE goes also with the identification of selected modules of gene activation in distinct individuals. Very strong signals indicate that type I interferon (IFN) may contribute to autoimmunity in a large proportion of SLE individuals and therapeutic trials targeting IFN signaling suggest the clinical relevance of this mediator. B cells/plasmablasts are also relevant and obvious targets. Refinements in our understanding in B cell sub setting and/or the timing in disease development in which they play a relevant role should result in defining the appropriate targets specific to this cell lineage. Gene modules activated during flares suggest that neutrophils in a subset of individuals may also be relevant targets. Cytokine affecting T cell differentiation, in particular T follicular helper cells, represent additional relevant targets.
Within the last several years a number of novel biological targets have been identified in SLE. However, a single biological agent has been approved for SLE treatment in the last five decades. This underlies the difficulties encountered when translating validated targets in efficacious therapeutic agents. This stress the need for careful preclinical evaluation. It further emphasizes the need of small phase II clinical trials based on stringent inclusion criteria aiming at precisely identifying individual groups more likely to respond to validate the target. Current progress made in the identification of molecular signatures in individuals with SLE will offer the tools for the requested accurate selection.
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SP0085 PATIENT REPORTED OUTCOMES

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In SLE as in other rheumatic diseases, the most relevant target of intervention should be a status with controlled disease process assuring no further accrual of damage. If actual expert discussions like DORIS define the frame of such a status, clinical activity measured by a validated lupus disease activity instrument, serologic activity and therapy – because of harm - are the dimensions of remission with its duration as additional factor for outcome. Patient reported outcomes (PROs) were not included. Otherwise, if payers and reimbursement system decide about relevance, patient outcomes are clear of highest importance as target.
Looking on the evidence of PROs for outcome in SLE, PROs were never used as primary endpoint in clinical trials. In RCTs, PROs were often collected and mostly explorative analysed. There is no evidence that PROs can validly define the above described status of controlled disease. But from systematic analyses in RA, we know that pure PRO like VAS of general health status and semi PRO like tender joints are at least as relevant as more "objective" criteria like swollen joints or CRP as clearly exhibited by the ACR/Eular remission criteria for RA.
The challenge in SLE is that the discrepancies between patients' and physicians' perception and perspectives are even more distinct than in RA. Sometimes, there is the expression that physicians and patients are describing different diseases. The burden of illness in lupus is better defined by pain than by organ manifestations; the overall survival in SLE is more related to lupus nephritis than to fatigue. It is obvious that physicians should analyse the actual clinical symptoms and integrate the future consequences of their actual management in their decision, and patients are more focused on release of their actual burden.
Until today, these different and divers perspectives are no integrated, neither in RCTs nor in daily care. But such integration is mandatory, because no side imagines the complete picture of lupus, which may also produce to the poor results of clinical trials. In routine care, this behaviour causes frustration and mental distress, optimal results are prohibited.
So, the answer to what is more relevant in the management of SLE patients - clinical targets, biological targets or PROs – is the integration of all important aspects of lupus. This implies more than the statistical evaluation of the best items of all three aspects, it is the active involvement of patients in their care: patient empowerment in SLE, a fruitful process, in which both sides have to learn a lot from and about each other.
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Joint EULAR - EFIS session: Tilting the balance: from disease to tolerance induction

SP0086 PATHOGENIC MEMORY CELLS: ROAD BLOCKS TO TOLERANCE INDUCTION?

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While conventional state-of-the-art immunosuppression can lead to significant