FRIDAY, 15 JUNE 2018

Advances in biologic therapy of small vessel vasculitis

SP0119 THE EVOLVING ROLE OF MEPOLIZUMAB IN EGPA

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There is overwhelming evidence that eosinophiles play a key role in the pathogenesis of EGPA. IL-5 is the central cytokine for eosinophil maturation, eosinophil release from the bone marrow and eosinophil survival. Mepolizumab is an antibody neutralising IL-5, which proved efficient in the hypereosinophilic syndrome and eosinophilic asthma, amongst other conditions. Targeting this cytokine in EGPA therefore seemed plausible. Two small uncontrolled trials demonstrated the safety of mepolizumab in EGPA and indicated the potential for induction of remission, maintenance and steroid sparing. A randomised controlled trial (MIRRA) confirmed those findings and showed higher rates of accrued remission for mepolizumab when given as ad-on medication to conventional immunosuppressants and/or glucocorticoids. Steroid sparing properties were also confirmed. MIRRA and previous trials in different indications issued no major safety concerns. Based on this trial drug approval for EGPA might be feasible.

To date the major problems in the treatment of EGPA are 1) refractory disease 2) a high frequency of relapses and 3) the need for high glucocorticoid doses in many patients.

Mepolizumab could be used for induction of remission in addition to glucocorticoids. However, its not yet clear, which subgroup of patients might profit most. Especially patients with severe disease have not been investigated. For patients with refractors non-severe disease mepolizumab is a potential option. Mepolizumab also was efficient in preventing relapses and therefore may also be used for maintenance of remission, especially in patients suffering from prevalent relapses. Finally, patients with high need for glucocorticoids could profit from mepolizumab, particularly in case of steroid-sensitive comorbidities or steroid-induced complications.

Disclosure of Interest: F. Moosig Consultant for: Chugai, GSK
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SP0120 CURRENT CONTROVERSIES IN THE USE OF RITUXIMAB FOR INDUCTION AND MAINTENANCE OF AAV DISEASE

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Rituximab has now taken one of the first places in induction remission treatment of ANCA-associated vasculitides (AAVs) and is challenging cyclophosphamide. Rituximab is an anti-CD20 IgG1 mouse-human chimeric antibody that selectively depletes mature and memory B-cells.

Use of rituximab for induction

In AAVs, rituximab non-inferiority to cyclophosphamide as induction agent was clearly established. In the RAVE trial, which compared oral cyclophosphamide to rituximab as induction regimen, the remission rate at 6 months was 64% in the rituximab group and 53% in the cyclophosphamide group. Consequently, rituximab has revolutionised AAVs' standard-of-care and is now recommended as first-line therapy for many patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

The RAVE trial prospectively compared two arms: induction with glucocorticoids combined with oral cyclophosphamide for 3–6 months followed by 12–15 months of azathioprine versus glucocorticoids and rituximab (375 mg/m²/week for 4 consecutive weeks) followed by placebo. At 12 and 18 months respectively, 48% and 39% of the rituximab–placebo recipients had sustained complete remission vs. 39% and 33% of the cyclophosphamide–azathioprine group. Those outcomes demonstrated that, after rituximab induction, azathioprine maintenance therapy is not useful. Nonetheless, both groups still had very high relapse rates, meaning that an effective maintenance regimen had not yet been found.

In contrast, these findings in induction phase could not be applied to AAVs forms excluded from the RAVE study, i.e. EGPA, vasculitis associated with anti-glomerular basement membrane antibodies (Goodpasture's syndrome), patients with alveolar haemorrhage requiring mechanical ventilation or those with rapidly progressive renal failure with creatinine exceeding 350 micromol/L. Also, studies are lacking to demonstrate that rituximab should be recommended as first-line therapy for patients who do not require cyclophosphamide for remission induction or patients with predominant granulomatous manifestations (granulomatous ear, nose and throat (ENT) lesion(s), isolated tracheal or bronchial stenosis, orbital tumour or pachymeningitis) that are life-and/or function-threatening.

Use of rituximab for maintenance

The idea to maintain remission with low-dose rituximab every 6 months for 18 months seemed reasonable than no intervention, as shown by MAINRITSAN trial results. In that prospective RCT, rituximab maintenance consisted of semestrial 500 mg infusions for 18 months. The first rituximab infusion was given 3–4 weeks after the end of cyclophosphamide induction therapy, followed by the second 2 weeks later and semestrial infusions thereafter. At the end of follow-up, 28 months post-randomization and 10 months after the last rituximab infusion, 5% of rituximab recipients vs. 28% of azathioprine-treated patients had relapsed. Prolonged follow-up of those patients showed that, at 60 months, although relapses had occurred in both groups, rituximab remained superior to azathioprine for sustaining remission. Although the results highlighted rituximab superiority in maintaining remission, it also became clear that relapses still occurred, frequently 18 to 24 months after the last rituximab infusion.

An answer to the optimal rituximab duration will be partially obtained with the MAINRITSAN 3 trial (ongoing), which is comparing, after randomization, four additional semestrial rituximab infusions (500 mg) to placebo, after patients had previously received rituximab during 18 months. It seems reasonable that, in the future, treatment duration will be adapted to prognostic factors and predictors of relapses.

Also, the impact of using higher dose of rituximab during maintenance will be addressed by the RITAZAREM trial (ongoing). This protocol evaluates rituximab infusions of 1 gram every 4 months for 20 months compared to oral azathioprine.

Use of rituximab for EGPA

Data on rituximab's clinical benefits for eosinophilic granulomatosis with polyangiitis (EGPA) patients is currently restricted to low-evidence-based open-label studies and case reports. The main findings of these studies indicate a potential benefit in severe refractory/relapsing EGPA, especially in patients with positive ANCA. Two ongoing prospective studies in France are comparing rituximab to conventional immunosuppressants as induction (REOVAS trial) and maintenance phase (MAINRITSEG trial). It will help to define more precisely the indication of rituximab in EGPA patients and eventually highlight which patients would benefit from the drugs.

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Tapering and flaring in PsA and SpA

SP0121 TAPERING IN PSA – TO DO OR NOT TO DO?

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This talk will discuss the current evidence regarding tapering or drug withdrawal in patients with psoriatic arthritis. With increasing numbers of patients achieving good outcomes such as remission, the issue of how long to continue treatment for has been raised. Given the cost of some of the newer therapies, this question also has significant cost effectiveness implications.

There is a limited amount of evidence but data from randomised and observational studies will be discussed as well as key research questions that remain outstanding.

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SP0122 TAPERING IN AXIAL SPONDYLOARTHRITIS – TO DO OR NOT TO DO?

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According to the current version of the ASAS-EULAR management recommendations for axial spondyloarthritis, tapering of a biological disease modifying anti-rheumatic drug (bDMARD) can be considered once a remission is achieved. Tapering is opposed to a complete discontinuation that is associated with a very high disease flare risk (70%–100%) in axial spondyloarthritis. The question of tapering in axial spondyloarthritis has been addressed in a number of small clinical trials: in the majority of the them, tapering (either dose reduction or increase of the injection/infusion interval) could be done without a disease flare. It is, however, not clear, whether the tapering has any beneficial effect for a patient (i.e., in terms of safety) in addition to a cost-saving effect. Further, a number of questions related to tapering still requires an evidence-based answer: a) what is the optimal time-point of the initiation of tapering (e.g. 3, 6 or 12 months after remission achievement)? b) what is the optimal tapering regimen? c) are there reliable predictors of sustained remission/disease flare during tapering? The question of a bDMARD tapering after remission achievement will be at least partially answered in ongoing

phase 4 trials with TNF blockers in non-radiographic axial spondyloarthritis. An appropriately designed and powered long-term trial is needed to investigate possible long-term benefits and risks of treatment tapering in axial spondyloarthritis.

Disclosure of Interest: None declared

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Prevention of OA: yes we can!

SP0123 WHY IS THE PREVALENCE OF KNEE OSTEOARTHRITIS INCREASING?

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Invited speaker abstract submission

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WHY IS THE PREVALENCE OF KNEE OSTEOARTHRITIS INCREASING?

D. Felson

I will give my lecture on: Friday, 15 June 2018

Disclosure of Interest: None declared

Populations throughout the world are ageing and with ageing comes an increase in knee osteoarthritis. The prevalence of obesity is also rising and this further contributes to an increased risk of disease. Not surprisingly, the demand for knee replacements is rising quickly and is projected to increase further.

While the increase in osteoarthritis may be due in part to ageing and obesity of the population, there may be other causes. In a recent study, cadavers whose age and weight at the time of death were known were examined for evidence of knee osteoarthritis. It was found that, after adjustment for age and weight, knee osteoarthritis in our current postindustrial era was twice as common as knee osteoarthritis in the early industrial era. Reasons for this increase include changes in diet or in physical activity. They might also include changes in effects or severity of obesity. Understanding the increase in prevalence might provide new clues to osteoarthritis prevention.

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SP0124 PHYSICAL ACTIVITY AND EXERCISE: OPPORTUNITIES AND CHALLENGES

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Osteoarthritis (OA) is a steadily growing public health concern in particular as there is still a lack of curative therapeutic options in a biological sense. Thus, prevention of OA becomes an increasingly important topic.

Physical activity, and exercise are among the key modifiable risk factors associated with OA. Joints are built to be used, but overuse and joint injuries are also linked with incident OA. This presentation will provide some key opportunities with exercise to maintain joint health, but also the challenges when the window of opportunity is exceeded.

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Big data for musculoskeletal research

SP0125 HOW BIG DATA AND MACHINE LEARNING COULD CHANGE THE GAME

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With recent advances in the acquisition and digitisation of medical data, the use of routinely collected health data for research is on the rise. Routinely collected data comes with the promise of the 3 V's of "big data": volume, velocity, and variety. Recent recommendations by the UK National Institute for Health and Care Excellence and the Academy of Medical Sciences have therefore acknowledged the potential for data science methods to play an increasingly important role in healthcare research.

Against this backdrop of growing data and increasing computational resources, the use of data science methods including machine learning is becoming popular for analysing large-scale medical datasets.

This talk provides a brief overview of machine learning methods for healthcare applications including an introduction to supervised and unsupervised learning, followed by real-world examples of data analysis using machine learning, such as (a) the development of prognostic models for clinical risk assessment, and (b) mining of electronic health records for detecting patterns and phenotypes within a population.

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SP0126 BIG DATA FOR TREATMENT EFFECTIVENESS AND SAFETY

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While randomised clinical trials remain the gold-standard for examining drug-effects, there are limitations to the evidence they provide. For example, studies are usually too small or too short to detect rare and long-term adverse effects. This is particularly true for kidney-related outcomes where many trials were under-powered to detect outcomes of interest such as end-stage renal disease, too historic to collect data on newly-defined entities such as acute kidney injury or simply excluded patients with chronic kidney disease. In addition, disproportionate recruitment of Caucasian men in mid- to older-life limits the evidence base for understanding risk of adverse-effects in other population groups such as women, the elderly and people of non-Caucasian ethnicity. Determining these outcomes requires long-term surveillance of population databases, usually anonymised health care records, once a drug is in routine use.

In this talk I will discuss recent work from our group where we have used routinely collected renal function measurements from primary care to precisely examine kidney-related and other adverse effects. I will discuss some of the difficulties of this approach as well as the potential it offers to understand better the balance between risks and benefits of many drugs in common use.

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From big data to personalised medicine in paediatric rheumatic diseases

SP0127 FROM MENDELIOME TO PERSONALISED MEDICINE IN CHILDHOOD SLE

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Pediatric-onset SLE is a rare condition where genetics traits are believed to play an important causal role. A few monogenic causes of SLE have been described mostly in familial forms, including complement deficiencies, so-called type I interferonopathies, and B cell-related defects. Genetic studies in mouse models and genome-wide associations studies in patients have also pointed to other genes potentially involved in juvenile SLE. However, large-scale sequencing analyses of paediatric SLE are lacking, and the overall contribution of genetic factors in disease onset is therefore unknown. Personalised medicine relies on the understanding of underlying mechanisms. Genetic discovery and functional characterization of the variants prefigure the precision medicine in complex diseases such as SLE.

We have designed a NGS panel comprising genes for which mutations are known lupus causing (KLC) (also reported as the Mendeliome) as well as prospective candidate genes, potentially lupus causing (PLC), and analysed 117 children who fulfilled ACR criteria for SLE from two large cohorts of pediatric-onset SLE in the UK and France. Genetic variants were identified and filtered to select rare (ExAC database frequency of <1% for homozygous variants and <0.01% for heterozygous variants) and predicted *in silico* as damaging by different algorithms.

We identified mutations in KLC genes for 8 patients. Variant segregation within families and functional analyses supported the causal role of these mutations. Other patients had monoallelic variants in recessive KLC genes, which may have contributed to disease onset and other patients displayed rare and pathogenic variants in PLC genes. This enrichment was specific to the lupus cohort compared to a control cohort of healthy patients.