Opening session (live-streamed with external Q&A)

Keynote

B CELLS AS A THERAPEUTIC TARGET IN SLE: WHERE WE ARE TODAY AND WHERE WE MAY BE TOMORROW

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Systemic lupus erythematosus (SLE) is a heterogeneous disease characterised by abnormalities in cellular and humoral immunity with clear hints that abnormalities of B lineage cells (B and plasma cells) are key drivers.

Clinical experiences with belimumab as a first approved targeted SLE treatment provide robust evidence that blocking BLyS/BAFF selectively interfering with B cell survival can change the course of the disease, including prevention of damage accrual. Recent failures of first generation anti-CD20 (rituximab, ocrelizumab) and BTK inhibitors (fenebrutinib/GDC-0853 and evobrutinib3) together with the occurrence of aner-gic B cells and plasma cells) are key drivers.

In addition, enhancing regulatory B-cell functions may hold attractive opportunities. Such strategies have potential to reinstall the balance of pathogenic and protective B cells with the potential of more specific therapies. Moreover, these treatment targets should have the potential to overcome the status of anergic B cells holding promise to escape the detrimental chronic autoimmune process. In this context, targeting checkpoint molecules that downmodulate intracellular phosphatases, such as CD40 or other targets of this family on B cells, and enhancing Treg cells, may provide the rational for various innovative strategies. These include more profound targeting by second generation anti-CD20 modalities (obinutuzumab) CD19 (CART, bispecific antibodies) or employing other immune targets, such as CD38 (daratumumab), or BAFFR (talamumab).

Since its development in the 1950s, the vitamin K (VKA) antagonist warfarin has been a standard anticoagulant, which for 40 years has utilised the International Normalisation Ratio (INR) to regulate the required dose. Although effective in the treatment of blood clots and reducing the risk of stroke in atrial fibrillation, its use necessitates significant food restrictions and the avoidance of many types of drugs. In contrast, direct oral anticoagulants (DOACs) are fixed-dose, more predictable, require no routine monitoring, have no interactions with food or alcohol and many fewer drug interactions than warfarin. The RAPS study demonstrated that rivaroxaban is not inferior to warfarin in the treatment of patients with venous thromboembolism with a target INR of 2–3.1 Quality of life consideration favoured rivaroxaban in that study. Notably, 27% of the patients in this trial were triple positive for antiphospholipid antibodies (APAbs). In contrast, direct oral anticoagulants (DOACs) are fixed-dose, more predictable, require no routine monitoring, have no interactions with food or alcohol and many fewer drug interactions than warfarin.

In contrast, in the TRAPS trial, patients with high risk triple-positive antiphospholipid syndrome (APS) on rivaroxaban were shown to be at increased risk of developing thromboembolic events—a concern mirrored by a report from Ordi-Ross et al, although the numbers of arterial events comparing rivaroxaban and warfarin was not in fact statistically significantly different.3 In addition, there are several early studies reporting approximately 3% of patients per year develop recurrent thrombosis while on warfarin.4

Currently, the Medicine and Healthcare Products Regulatory Agency (MHRA) in the UK advise that DOACs are not recommended for patients with a history of thrombosis who are diagnosed with APS and particularly for those who are triple positive. DOACs may, however, be considered in patients
who have difficulty achieving a target INR despite compliance with warfarin. EULAR recommendations indicate that rivaroxaban should not be used in APS patients with triple APAbs positivity. However, there is an ongoing need for a prospective evaluation of DOACs versus VKA inhibitors in patients with provoked venous thromboembolism, particularly in those without triple positive disease. The ongoing RISAP study (NCT03684364) is comparing patients with APS with single/double positivity only for APAbs, who have a history of ischaemic stroke or other brain ischaemic injury. The endpoint is the rate of change in brain white matter hyperintensity volume between baseline and 24 months follow-up assessed on magnetic resonance imaging as a surrogate marker of ischaemic damage.

In summary, DOACS are not dead...... but their ‘existence’ in APS/systemic lupus erythematosus is threatened!

REFERENCES

Learning Objectives
• Explain that while widely used VKAs, notably warfarin, while often effective, have major drawbacks in terms of requirement for regular blood tests, and the avoidance of many types of food and drugs
• Describe how the RAPS study demonstrated the comparative effectiveness of rivaroxaban compared to warfarin in treatment with venous thromboembolic disease with a target INR of 2–3
• Describe how the TRAPS and later studies identified a risk of thromboembolic disease in patients on DOACs compared to warfarin in triple APAB positive patients, although earlier studies demonstrated that there is an increased risk (about 3% per annum) of recurrent thromboembolic risks on warfarin
• Explain, whilst the current advice from the MHRA and EULAR is to avoid DOACs in the treatment of triple positive APS patients, there remains a desperate need for clinical trials to compare the effectiveness of DOACs with VKAs in single and double positive antiphospholipid antibody APS

09 COVID-19 VACCINE IN LUPUS PATIENTS
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CoronaVac (SARS-CoV-2 inactivated vaccine) has been largely used as the main immunogen for COVID-19 in several countries; however, its immunogenicity, antibody decay and booster dose response in immunocompromised individuals has not been established. 1–3

This Phase 4 prospective controlled study of 910 patients with adult autoimmune rheumatic diseases (ARD) and 182 age- and sex-controlled group (CG) subjects who received two doses of CoronaVac in a 28-day interval. The primary outcome was assessed by anti-SARS-Cov-2 IgG and neutralizing antibodies 6 weeks after the second dose. Secondary outcomes included immunogenicity at different time points, antibody decay, booster dose response and vaccine safety.

Pre-specified endpoints were met, with lower anti-SARS-Cov-2 IgG seroconversion (70.4% versus 95.5%, p<0.001) and frequency of neutralizing antibodies (56.3% versus 79.3%, p<0.001) in patients with ARD compared to the CG.1 A significant decline in the number of COVID-19 cases (p<0.0001) was observed 10 days after the second dose, with a predominant P1 variant. Six months after the 2nd dose of CoronaVac, anti-S1/S2IgG positivity reduced 23.8% in patients with ARD (p<0.001) and 20% in the CG (p<0.001). A concomitant decrease of COVID-19 cases (from 27.7 to 8/100 person-years; p<0.001) occurred during this period. The booster dose after 6-months resulted in a significant increase in anti-S1/S2 IgG rates (60% versus 93%, p<0.0001), neutralising antibody positivity (38% versus 81.4%, p<0.0001), GMT (25.3 versus 140.5 AU/mL, p<0.001) and NAb activity (69.7% versus 90.1%, p<0.001). Safety analysis revealed no moderate/severe adverse events. Multivariate analysis revealed that drugs were the major factors influencing immunogenicity, antibody decay and third dose response.

In conclusion, CoronaVac has an excellent safety profile and reasonable rates of quantitative serology/neutralisation in ARD patients. A moderate antibody waning occurred over six months with a decline in cases despite the Delta variant spread. Booster dose at six months induced a robust response. Our data suggest that CoronaVac vaccine is an excellent alternative treatment for COVID-19 in immunocompromised patients. [clinicaltrial.gov #NCT04754698 (CoronavRheum); Funded by FAPESP, CNPq and B3 - Bolsa de Valores do Brasil].

REFERENCES

Learning Objectives
• Discuss Covid–19 vaccine immunogenicity in ARD patients
• Identify the risk factors for reduced COVID–19 vaccine response
• Define vaccine antibody waning in ARD patients and their risk factors
• Manage the third dose of COVID–19 vaccine in ARD patients

10 NOVEL CONCEPTS IN SLE: IS IT TIME FOR A NEW TAXONOMY?
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