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COMPREHENSIVE GENETIC AND FUNCTIONAL ANALYSES OF FC GAMMA RECEPTORS EXPLAIN RESPONSE TO RITUXIMAB THERAPY FOR AUTOIMMUNE RHEUMATIC DISEASES


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Background: Rituximab is widely used to treat rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) but clinical response varies. Efficacy is determined by the efficiency of depletion, which may depend on a variety of FC gamma receptor (FcγR)-dependent mechanisms. Previous research was limited by complexity of the FcγR locus, not integrating copy number variation with functional SNP and small sample size.

Objectives: The study objectives were to assess the effect of the full range of FcγRs variants on depletion, clinical response and functional effect on NK-cell-mediated killing in two rheumatic diseases with a view to personalised B-cell depletion therapies.

Methods: A prospective longitudinal cohort study was conducted in 873 patients [RA=611; SLE=262] from four cohorts (BSRBR-RA and BILAG-BR registries, Leeds RA and Leeds SLE Biologics). For RA, the outcome measures were 3C-DSAS28CRP and 2C-DSAS28CRP at 6 (+/-3) months post-rituximab (adjusted for baseline DAS28). For SLE, major clinical response (MCR) was defined as improvement of active BILAG-2004 domains to grade C/better at 6 months. B-cell depletion was evaluated by highly-sensitive flow cytometry. Qualitative and quantitative polymorphisms for five major FcγRs were measured using a commercial multiplex ligation-dependent probe amplification. Median NK cell FcγRIIIa expression (CD3-CD56+CD16+) and NK-cell degranulation (CD107a) in the presence of rituximab-coated Daudi/Iraj B-cell lines were assessed using flow cytometry.

Results: In RA, for FCGRA3, carriage of V allele (coefficient -0.25 (SE 0.11); p=0.04) and increased copies of V allele (-0.20 (0.09); p=0.02) were associated with greater 2C-DSAS28 response. Irrespective of FCGRA3 genotype, increased gene copies were associated with a better response. In SLE, 177/262 (67.6%) achieved BILAG response [MCR=34.4%; Partial=33.2%]. MCR was associated with increased copies of FCGRA3-158V allele, OR 1.64 (95% CI 1.12-2.41) and FCGRA2-ORF allele 1.93 (1.09-3.40). Of patients with B-cells data in the combined cohort, 296/415 (57%) achieved complete depletion post-rituximab. Only heterozygosity for FCGRA3-158V and increased FCGRA3-158V copy number were associated with increased odds of complete depletion. Patients with complete depletion had higher NK cell FcγRIIIa expression at rituximab initiation than those with incomplete depletion (p=0.04) and this higher expression was associated with improved EULAR response in RA. Moreover, for FCGRA3, degranulation activity was increased in V allele carriers vs FF genotype in the combined cohort; p=0.02

Conclusion: FcγRIIIa is the major low affinity FcγR and increased copies of the FCGRA3-158V allele, encoding the allotype with a higher affinity for IgG1, was associated with clinical and biological responses to rituximab in two autoimmune diseases. This was supported by functional data on NK cell-mediated cytotoxicity. In SLE, increased copies of the FCGRA2-ORF allele was also associated with improved response. Our findings indicate that enhancing FcγR-effector functions could improve the next generation of CD20-depleting therapies and genotyping could stratify patients for optimal treatment protocols.

REFERENCES: None

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Methods: We conducted a rapid review to investigate the role of PPI in guideline implementation. We searched the following databases - Medline, Embase, Cinahl, and two large repositories - WHO, G-IN). A comprehensive search for relevant literature was undertaken (three databases - Medline, Embase, Cinahl, and two large repositories - WHO, G-IN). A priori eligibility criteria and systematic review-based methods were used to identify primary studies with explicit reference to PPI involvement in a rheumat/musculoskeletal - MSK guideline implementation activity. Extracted data from included studies was interrogated for details regarding activities, contexts, outcomes, and impact of PPI in guidelines implementation and further discussed in review project meetings.

Results: Ten papers were included, only 1 from the global south. A prevalence of consultative PPI activities in guidelines dissemination (e.g., language translations, patient versions) was found. Few studies explicitly report high-level PPI engagement in relation to care pathway adjustments, care commissioning, institutional operations and policy with a view to MSK guideline implementation.

Training, development, and practice of PPI in MSK guideline implementations were not evidenced to have spread much beyond Europe and are also not well reported in literature nor rightly accrued as PPI activities in guideline implementation. The alliance framework (Figure 1) highlighting an iterative process of "creative thinking/co-production" and "strategic doing" helps to conceptualise PPI in MSK guideline implementation. The framework guides knowledge translation from guidelines to real world practice and aims to drive quality improvement for MSK care with patients, for patients, across and within care settings globally.

Conclusion: Despite success of PPI in rheumatology/MSK research, oversight or ineffective PPI in guideline implementation may hamper translation of novel advances in MSK care into real world practice and patient benefit. The alliance framework prioritises effective and meaningful PPI in MSK guideline implementation design, delivery, and evaluation, ideally applied in parallel with the development of evidence-based guidance recommendations. It highlights continuous application of innovative thinking, dynamic, and impactful collaborations for bridging the evidence-practice gap and improving quality of care for MSK patients globally through novel partnerships.

Disclosure of Interests: None declared

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Vaccination in rheumatic diseases with lessons from COVID

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SEREOLOGICAL RESPONSE AND SAFETY OF A THREE-DOSE SARS-COV-2 VACCINATION STRATEGY IN PATIENTS WITH IMMUNE-MEDIATED INFLAMMATORY DISEASES ON IMMUNOSUPPRESSIVE THERAPY

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Background: Patients with immune-mediated inflammatory diseases (IMIDs) on immunosuppressive therapy have an inadequate serologic response following two-dose SARS-Cov-2 vaccination, and a standard vaccination strategy of three doses for this patient group is currently under implementation in several countries. However, the serological response and safety of this strategy has not been evaluated.

Objectives: To assess serological response and safety of a three-dose vaccination strategy in IMID patients on immunosuppressive therapy as compared to standard two-dose vaccination of healthy controls.

Methods: The prospective observational Nor-vaC study (NCT04798625) enrolled adult patients on immunosuppressive therapy for inflammatory joint- and bowel diseases. Healthy controls were health care workers from participating hospitals. All participants received standard vaccines according to the national vaccination program with three doses in patients and two doses in controls. The third dose was offered to IMID patients >4 weeks after the second dose. Analyzes of antibodies binding the receptor-binding domain of the SARS-Cov-2 Spike protein were performed prior to, and 2-4 weeks after the second and third vaccine doses. Levels were compared across groups by Mann-Whitney U tests and multi-variate linear regression was used to identify predictors of response.

Results: Overall, 961 patients (315 rheumatoid arthritis, 156 spondyloarthritides, 171 psoriatic arthritis, 132 ulcerative colitis and 182 Crohn’s disease) (median age 54 years [IQR 43-64]; 56 % women and 227 controls (median age 44 years [IQR 32-55]; 83 % women) were included in the present analyses. TNF monotherpay was used by 399 patients, 229 used TNF in combination with other immunomodulators, 189 methotrexate monotherapy, 39 vedolizumab, 23 JAKi and 73 patients used other drugs. Patients on rituximab were not included. Patients were vaccinated with Pfizer BNT162b2 (54% patients, 14% controls), Moderna mRNA-1273 (16% patients, 40% controls) or a combination of vaccines (30% patients, 46% controls). Patients received the third vaccine dose a median of 120 (IQR 102-143) days after the second dose. After two doses, median anti-Spike antibody levels were significantly lower in patients (861 BAU/ml (IQR 418-4275) than controls (6318 BAU/ml (IQR 2468-9857), p<0.001 (Figure 1).

Following the third dose, patients achieved antibody levels comparable to the two-dose vaccinated controls (median 5480 BAU/ml (IQR 1081-12069), p=0.28) (Figure 1). In the patients anti-Spike antibody levels increased by a median of 2969 BAU/ml (IQR 2659-9129) from the second to the third dose. Main factors associated with increased antibody level after the third dose were younger age (β =-8.77 (p=0.002)), and vaccine status (mRNA-1273 vaccine (β =549 (p<0.001)) or a combination of vaccines (β =4367 (p<0.001)).

Adverse events were reported by 438 (48%) of patients after the third dose as compared to 471 (54%) after the second dose and 193 (78 %) of controls. Disease flares were reported by 42 (5%) and 69 (8%) patients after the second and third dose, respectively.

Conclusion: This study suggests that a third vaccine dose for immunosuppress- prescribed patients closes the gap in serological response between patients and