Expert Review of Clinical Immunology

ISSN: 1744-666X (Print) 1744-8409 (Online) Journal homepage: http://www.tandfonline.com/loi/ierm20

Belimumab and antipneumococcal vaccination in patients with systemic lupus erythematosus

Tudor Azoicai, Sabina Antoniu, Irina Draga Caruntu, Doina Azoicai, Ileana Antohe & Cristina Gavrilovici

To cite this article: Tudor Azoicai, Sabina Antoniu, Irina Draga Caruntu, Doina Azoicai, Ileana Antohe & Cristina Gavrilovici (2018): Belimumab and antipneumococcal vaccination in patients with systemic lupus erythematosus, Expert Review of Clinical Immunology, DOI: 10.1080/1744666X.2018.1429269

To link to this article: https://doi.org/10.1080/1744666X.2018.1429269

Accepted author version posted online: 16 Jan 2018.
Published online: 22 Jan 2018.

EXPERT REVIEW OF CLINICAL IMMUNOLOGY, 2018
https://doi.org/10.1080/1744666X.2018.1429269

Taylor & Francis
Taylor & Francis Group

KEY PAPER EVALUATION

Belimumab and antipneumococcal vaccination in patients with systemic lupus erythematosus

Tudor Azoicai[a], Sabina Antoniu[b], Irina Draga Caruntu[a], Doina Azoicai[c], Ileana Antohe[b] and Cristina Gavrilovici[d]

[a]Department of Morpho-functional Sciences, University of Medicine and Pharmacy "Grigore T Popa", Iasi, Romania; [b]Department Medicine II-Nursing, University of Medicine and Pharmacy "Grigore T Popa", Iasi, Romania; [c]Department of preventive medicine and interdisciplinarity, University of Medicine and Pharmacy "Grigore T Popa", Iasi, Romania; [d]Department Medicine III, University of Medicine and Pharmacy "Grigore T Popa", Iasi, Romania

ABSTRACT

In systemic lupus erythematosus (SLE), flares can be caused by infections. In particular, *Streptococcus pneumoniae* infection can be severe or even potentially lethal in absence of previous immunization or in case of 'aggressive' systemic antibiotic therapy. Immunization efficacy, however, can be reduced in such patients with the use of the various immunosuppressive therapeutic regimens. In particular, the use of novel monoclonal antibodies against B lymphocytes raises concerns over the potential interference with antipneumococcal vaccination. Previous studies demonstrated that belimumab therapy did not significantly reduce the efficacy of antipneumococcal vaccination, when received after the initiation of belimumab therapy. The study being evaluated in this article investigated the efficacy of vaccination in relationship to initiation of belimumab therapy in SLE patients.

ARTICLE HISTORY
Received 2 December 2017
Accepted 15 January 2018

KEYWORDS
Antibody; antipneumococcal; belimumab; systemic lupus erythematosus; serotype; Streptococcus pneumoniae

1. Methods and results

This was a phase IV open label multicenter study performed in the USA in two cohorts of SLE patients: one cohort (pre-belimumab cohort) received pneumococcal vaccine (Pneumovax 23®) before initiating belimumab therapy, whereas the second was given the same vaccine at Week 24 of belimumab therapy (belimumab concurrent cohort). The first cohort received nine doses of belimumab at weeks 4, 6, 8, and subsequently every 4 weeks to week 32. The second cohort also received nine doses of belimumab at baseline, weeks 2, 4 and subsequently every 4 weeks to week 28. The dosage was the same 10 mg/kg via intravenous infusion [1,2].

The primary end point was represented by the proportion of patients with positive response to anti-pneumococcal vaccine at 4 weeks from inoculation. Positive response was defined with a two-fold increase in antibody titers against at least one of the 23 serotypes as compared to pre vaccination levels or a post-vaccination antibody level of at least 0.6 mg/mL in patients with no pre-vaccination antibody titers.

Secondary end points were represented by the proportion of patients with positive responses to at least 11 of the 23 serotypes and by the proportion of patients with positive responses to at least 2, 3, 4, 5, 6, 8, 9, and 10 of the 23 serotypes. The secondary end points were analyzed post-hoc.

The primary end point was also analyzed in various population subsets according to the baseline use of antimalarial drugs (yes, no), baseline use of corticosteroids (>7.5 mg/day versus ≤7.5 mg/day), baseline use of any other immunosuppressive drugs (yes, no). The same sub-setting criteria were applied in another post-hoc analysis performed in patients with immune response to at least 12 of the 23 serotypes.

Safety end points were represented by immunogenicity (for belimumab), or by any various clinical or laboratory abnormalities reported after at least 8 weeks of vaccination. They were monitored prior to the first belimumab infusion in belimumab concurrent cohort and after vaccination but before the first belimumab dose in the pre-belimumab cohort. Belimumab-related safety end point was defined as treatment-emergent adverse event and was represented by any such effect occurring while on or after the first belimumab dose and not present before belimumab therapy.

The pre-belimumab cohort amounted to 34 patients whereas in the belimumab concurrent cohort 45 patients were included. Completion rate was 87.3%. In the overall cohort, 91.1% were females, and on combined immunosuppressant regimen 32.9% overall, 35.3% in the pre-belimumab cohort, and 31.1% in belimumab concurrent cohort.

The vaccine response rate at 4 weeks (the primary end point) was 97% in pre-belimumab cohort and 97.% in belimumab concurrent cohort. Of the two non-responders, one was in the pre-belimumab cohort and had a lower than normal pre-inoculation IgG titers, whereas the other was in the belimumab concurrent cohort and had normal baseline IgG titers. Both patients had a baseline combined regimen consisting of an antimalarial, corticosteroid, and an immunosuppressant and received less than 7.5 mg corticosteroid daily.

CONTACT Cristina Gavrilovici cristina.gavrilovici2012@gmail.com

Evaluation of: Chatham W, Chadha A, Fettiplace J, *et al*. A randomized, open-label study to investigate the effect of belimumab on pneumococcal vaccination in patients with active, autoantibody-positive systemic lupus erythematosus. *Lupus*. 2017; 26(14):1483-1490

The overall response rate to at least 10 serotypes was 85% and in post-hoc analyses the response rates to at least 12 of the 23 serotypes were comparable, 81.8% for pre-belimumab cohort and 78% in belimumab concurrent cohort. Response rates to at least 16 serotypes were 75.8% and 63.4%, respectively.

In pre-belimumab cohort, concomitant corticosteroid therapy with a daily dose of more than 7.5 mg/daily was associated with better response rate to at least 12 serotypes of the vaccine compared to patients receiving lower corticosteroid doses (90.9% versus 77.3%). In belimumab concurrent cohort, these were however comparable (77.3% versus 78.9%). Baseline immunosuppressive therapy was associated with lower response rates in both pre-belimumab and belimumab concurrent cohort (70.6% versus 93.8% in patients with no immunosuppressive therapy at baseline, 72.2% versus 82.6%, respectively).

Baseline IgA, Ig-G, and Ig-M level profiling was performed in responders versus non-responders to 50% of the serotypes and these levels were found to be lower on individual Ig basis in non-responders as compared to responders, although these levels were not lower than normal.

Safety analysis reported that 91.2% subjects in pre-belimumab cohort and 86.7% in belimumab concurrent cohort experienced at least one adverse event over the study period, arthralgia and nausea being the most frequent. The proportion of patients with belimumab-related side effect was 23.5% in pre-belimumab cohort and 8.9% in belimumab-24 cohort. The proportion of patients with vaccine-related adverse events was 4.4% in belimumab 24 cohort. No malignancies or death were reported and the proportions of patients experiencing non-fatal serious adverse events were 11.8% in pre-belimumab cohort and 6.7% in belimumab concurrent cohort. No immunogenicity was reported in either cohort.

2. Discussion

The prevalence of pneumococcal infection in SLE patients varies from 20 to 25 in 10,000 SLE patients and has a higher risk of manifesting as an invasive disease than in healthy population, the main cause being the therapeutic immunosuppression[3]. Furthermore in a Dutch study, the incidence of invasive pneumococcal infection was found to be 10-fold higher in SLE patients compared to healthy population [4]. Therefore, antipneumococcal immunization is indicated in SLE patients in order to mitigate this risk.

This study demonstrates that in SLE patients receiving belimumab therapy anti-pneumococcal vaccination is safe and effective, the only factor which would interfere with vaccine effectiveness being the use of immunosuppressant therapy prior to immunization. In fact, the majority of patients, prior of receiving belimumab or after receiving belimumab, responded in a comparable manner to >1 vaccine serotype. However, this primary end point does not appear to be the most appropriate in this setting, as most other studies including the response to more serotypes (e.g. 5, 6, 8. or 12)[5–7]. The use of response rate to at least 12 of the 23 serotypes, which was an end point of efficacy included in the post-hoc analysis, can be considered the most robust end point of the whole analysis because it further validates the other findings of this study.

The differences in vaccine reactivity noted in this study could have been influenced by the 'baseline' immunosuppression therapy which was given prior to belimumab. An unexpected finding was that of the *post hoc* analysis in pre belimumab cohort showing a better response rate to most of the serotypes in patients receiving higher corticosteroid doses: in concomitant belimumab cohort, vaccine response in higher corticosteroid dose subset was again lower than in corresponding pre belimumab cohort (78.9%).

3. Five-year view

One of the main causes of mortality reported in SLE patients is represented by infections. These can be facilitated by the impairments in the innate immunity which are the result of the disease itself and more importantly by immunosuppressors which are given in order to halt the progression of the disease. Most of such infections can only be treated once diagnosed but in some infections such as influenza, and infections with *S. pneumoniae* prevention via vaccination can be a more suitable therapeutic option. However, in such patients, vaccine seroconversion can be variable and suboptimal and this behavior does not always have one single cause.

One problem with these SLE patients is that they are usually receiving immunosuppressor regimens containing variable doses of corticosteroids and these are demonstrated to reduce the response to such vaccines making this prophylaxis practically useless. Therefore, in patients on prednisone doses of at least 20 mg daily vaccination is indicated only prior to corticosteroid initiation. This approach is supported by the results of a study demonstrating the significant reduction of influenza vaccine seroconversion in SLE patients receiving such doses of corticosteroids [8]. Interestingly antimalarial compounds such as hydroxychloroquine were associated with a better vaccine response [8]. In the study discussed by this article, the proportion of SLE patients on antimalarial therapy was higher in concomitant belimumab therapy and a subset analysis on vaccine response in these patients was not made available.

Another problem is related to vaccine response which in such patients can also be related the type of vaccine used. In healthy adults, antipneumococcal polyconjugate vaccine 13 (PCV13) unlike polysaccharide vaccine 23 (PPS23) is able to elicit initially a T-cell-dependent immune response which subsequently can trigger and maintain adequate protective antibody titers as a result of appropriate B-cell activation [7]. Furthermore, in the same category of adults, it has been observed that when PPSV23 was administered before PCV13, the immune response induced by PCV13 was reduced, and therefore, PCV13 should be administered first in patients who have not been previously vaccinated [6,7]. The same approach is recommended to be applied in immunocompromised hosts (patients with SLE belonging to this category) in order to maximize the protection against *S. pneumoniae* invasive infections[9].

However, in SLE patients receiving belimumab, only the efficacy of polysaccharide vaccine has so far been analyzed, and this was done in relation to the type of immunosuppressor medication used: SLE patients receiving concomitant belimumab therapy had antibody titers to this vaccine which were comparable to those found in healthy controls [10].

In another recent randomized placebo-controlled study performed in SLE patients receiving various concomitant immuosuppressors, the efficacy of a polysaccharide vaccine was compared against a combined sequential approach consisting of a polyconjugate vaccine (7-valent pneumococcal conjugate vaccine) followed by polysacharide vaccine. Both vaccine regimens were comparable in terms of 24 week seroconversion rate to at least 5 of the 7 serotypes shared in common by the two vaccine types[5].

Given that the main role of this vaccine is to protect against severe pneumococcal infection, it would be interesting and useful for clinical practice to evaluate both vaccines given according to the above-mentioned sequence not only in terms of immediate seroconversion but also in terms of duration of maintenance of protective antibody titers. Some of the most appropriate endpoints to consider in SLE on a long-term basis would be the incidence of invasive pneumococcal infections and the mortality rate due to pneumococcal infections.

This study highlights that on the one hand immunosupressor conventional therapy can be more adverse in terms of interference with protective effects of vaccination than belimumab and on the other hand that there is a need to develop vaccination schedules which should provide appropriate coverage on long-term basis.

Funding

This articles was not funded.

Declaration of interest

Tudor Azoicai received congress sponsorships from Pfizer, AbVie and BMS. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. A peer reviewer on this manuscript has disclosed they served as paid consultant for Glaxo Smith Kline. The other reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Human Genome Science Inc. aGC. A study to evaluate the effect of belimumab on vaccine responses in subjects with Systemic Lupus Erythematosus (SLE). In: ClinicalTrials.gov[Internet]. Bethesda(MD): National Library of Medicine (US). 2000-2017 Nov 19. Available from: https://clinicaltrials.gov/ct2/show/NCT01597492?term=NCT01597492&rank=1. NLM Identifier: NCT01597492. 2011 [19.11.2017]
2. Chatham W, Chadha A, Fettiplace J, et al. A randomized, open-label study to investigate the effect of belimumab on pneumococcal vaccination in patients with active, autoantibody-positive systemic lupus erythematosus. Lupus. 2017;26(14):1483–1490.
3. Schurder J, Goulenok T, Jouenne R, et al. Pneumococcal infection in patients with systemic lupus erythematosus. Joint Bone Spine. [Epub ahead of print]. 2017 May 18. pii: S1297-319X(17)30103-3.
4. Luijten RKMAC, Cuppen BVJ, Bijlsma JWJ, et al. Serious infections in systemic lupus erythematosus with a focus on pneumococcal infections. Lupus. 2014;23:1512–1516.

•• **excellent epidemiological study on morbidity and mortality of pneumococcal infection in SLE patients.**

5. Grabar S, Groh M, Bahuaud M, et al. Pneumococcal vaccination in patients with systemic lupus erythematosus: A multicenter placebo-controlled randomized double-blind study. Vaccine. 2017;35:4877–4885.

• **study comparing the efficacy of two vaccine regimens (sequential polyconjugate and polysaccharide versus polysaccharide alone).**

6. Greenberg RN, Gurtman A, Frenck RW, et al. Sequential administration of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults 60-64 years of age. Vaccine. 2014;32:2364–2374.

•• **excellent study on efficacy of the sequential vaccine regimen in healthy older adults (aged 60-64).**

7. Jackson LA, Gurtman A, van Cleeff M, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine. 2013;31:3577–3584.

•• **excellent study on efficacy of the sequential vaccine regimen in healthy older adults (aged 50-64).**

8. Borba EF, Saad CGS, Pasoto SG, et al. Influenza A/H1N1 vaccination of patients with SLE: can antimalarial drugs restore diminished response under immunosuppressive therapy? Rheumatology. 2012;51:1061–1069.
9. Rubin LG, Levin MJ, Ljungman P, et al. Infectious diseases society of A. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014;58:e44–100.
10. Nagel J, Saxne T, Geborek P, et al. Treatment with belimumab in systemic lupus erythematosus does not impair antibody response to 13-valent pneumococcal conjugate vaccine. Lupus. 2017;26:1072–1081.