The Journal of Rheumatology 2021;xx:xxxx
doi:10.3899/jrheum.201622

The Journal of Rheumatology

Editorial

The Results of Well-conducted Negative Clinical Trials Should Be Reported in a Peer-reviewed Journal

Roy Fleischmann[1]

We expect that the pathogenesis, manifestations, and successful management of disease will be fully reported in peer-reviewed journals. However, there are multiple publications addressing the likelihood that clinical trials that do not report a positive result are underreported in the medical literature, with a maximum of 50% of negative studies published, even after 5 years of availability of their results[1,2].

One way to think of the usefulness of our literature is as a road map. There are major "highways" (positive reports), "secondary roads" (major secondary considerations such as long-term safety and effectiveness), and "attractions" (opinions, historical correlations, etc.). But importantly, we need to be able to determine "detours and roadblocks" (well-performed negative studies), which are transparently reported.

In this issue of *The Journal of Rheumatology*, Genovese and colleagues report the results of a clinical trial exploring the efficacy and safety of poseltinib, a Bruton tyrosine kinase inhibitor (BTKi), which was found to be ineffective in the treatment of rheumatoid arthritis (RA) in a phase II study[3]. This is an important addition to our literature.

BTK is a tyrosine kinase that is encoded by the *BTK* gene in humans. In 1993 it was identified that *BTK* is the gene defective in primary immunodeficiency X-linked agammaglobulinemia. BTK is a member of the Tec family of nonreceptor tyrosine kinases and is expressed in all hematopoietic cells except T cells and terminally differentiated plasma cells. It has been shown that BTK has an important role in B cell differentiation *in vivo* and is involved in the regulation of the expansion and developmental progression of pre-B cells in the bone marrow. BTK is a crucial signal transducer of signals downstream of the IgM or IgG B cell antigen receptor in mature B cells governing proliferation, survival, and differentiation. For these reasons, BTK plays a crucial role in host defense and autoimmunity and it would be expected that BTK inhibition should affect mechanisms involving B cell– and non-B cell–mediated autoimmunity in RA and systemic lupus erythematosus (SLE) through the B cell receptor, Fc receptor, and RANK receptor signaling[4,5,6,7].

In a preclinical study[8], poseltinib showed promising results. It was found to irreversibly bind to and inhibit BTK effectively and inhibit the production of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β by human monocytes, as well as osteoclast formation by human monocytes. Poseltinib was also found to be effective in reducing the signs and symptoms of arthritis and preventing joint destruction in a murine collagen-induced arthritis model[8].

As reported by Genovese, *et al*, in this phase II study, several doses of poseltinib were evaluated in patients with active RA who had demonstrated either an inadequate response or loss of response to at least 1 disease-modifying antirheumatic drug (DMARD), whether a conventional synthetic DMARD or a biologic DMARD, or who had intolerance to one of these agents[3]. Poseltinib failed to meet the primary endpoint of achieving a statistically significant difference compared to placebo in the American College of Rheumatology 20 (ACR20) response, which is the best validated metric to determine whether a molecule is effective in RA in a placebo-controlled study[9].

Poseltinib did achieve ACR20 response rates of 55%, 44%, and 51% in the 5-mg, 10-mg, and 30-mg groups, respectively[3], which is consistent with percentages we have observed in similar patient populations in positive clinical studies with effective therapy. However, the ACR20 response was 48% in the placebo-treated subjects; thus, this study failed to demonstrate a statistically significant difference in the ACR20 response, strongly suggesting a lack of clinical effectiveness in RA. These results were seen in a predefined interim analysis and for this reason the study was terminated early.

Why is this manuscript worth publication if it is a failed study? The reason is precisely because it is a failed study of a

[1]*R. Fleischmann, Clinical Professor of Medicine, MD, Metroplex Clinical Research Center, Department of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA.*

The author declares no conflict of interest.

Address correspondence to Dr. R. Fleischmann, 8144 Walnut Hill Lane, Suite 810, Dallas, TX 75231, USA. Email: rfleischmann@arthdocs.com.

See BTKi (poseltinib) RA patient, *page xxx*

molecule with an attractive mechanism of action—differing from currently approved molecules in RA—with the potential to be effective in patients with RA who have failed other therapies.

There are multiple BTKi that have been developed for potential use in RA and studied in phase I trials over the past few years. These compounds include spebrutinib (CC-292), ABBV-105, evobrutinib, BMS-986142, PRN-1008 (rilzabrutinib), and acalabrutinib (ACP-196). Each of these phase I trials reported positive results without serious safety concerns and were suggestive that all achieved sufficient receptor occupancy with satisfactory pharmacokinetic (PK) and pharmacodynamic (PD) endpoints; they were also shown to be effective in animal models, where studied[5,10,11,12,13,14].

Each of these molecules was evaluated in prospective, placebo-controlled phase II studies in RA over the past several years. All failed to achieve their primary endpoint, but it is difficult to discover this information. Despite the wealth of information gathered, the results appeared only in abstracts at rheumatology meetings or on ClinicalTrials.gov; there have been no full manuscripts published in a peer-reviewed academic journal.

Why not?

As there are no full manuscripts, there are many unknowns: the full design of the studies, full inclusion and exclusion criteria, background medication that was or was not required, whether PK/PD assessments were conducted and if they matched what was seen in phase I, baseline demographics of the patients studied, whether secondary endpoints were met, the placebo response encountered and in which endpoints, where the studies were conducted geographically, whether the study sites were experienced in conducting studies in RA, any tolerability issues that were encountered, and so on. All these are important aspects of every study of BTKi that we need to know in order to determine whether the failure was due to the molecule itself, the lack of occupancy of the BTK receptor in a long-enough time period during the dosing schedule, or the pathway not being an effective one to target in RA.

With so much time, effort, and resources going into the development of BTKi in RA, understanding why these compounds failed is important. If it turns out that inhibition of the BTK pathway itself is not effective in the treatment of RA, but the molecules are effective in inhibiting the pathway, could they be used in combination with other mechanisms of action such as biologic or targeted synthetic DMARD, including inhibitors of TNF, IL-6, the co-stimulatory pathway, or Janus kinase inhibitors? As the mechanism of action is different, could any of these combinations substantially improve clinical responses without increasing safety or tolerability issues?

Why is this important?

There is an exception to the failure of multiple BTKi in the treatment of RA. Fenebrutinib has been reported to have positive results in both phase I and II studies in RA[15,16]. One might assume then, that the lack of efficacy of other BTKi is due to the molecules themselves and not to the effectiveness of inhibiting the BTK pathway. Spebrutinib covalently binds to BTK and irreversibly inhibits BTK, as does ABBV-105, evobrutinib, and BMS-986142, whereas rilzabrutinib and acalabrutinib do not. Fenebrutinib is a highly selective reversible BTKi that is noncovalently bound[17]. Is this the reason why fenebrutinib was successful while the others failed? This is potentially an explanation but would be hard to prove at present. What can be stated, however, is that the ACR20/50/70 responses seen in the trial with poseltinib[3] were generally similar to the fenebrutinib trial, but the placebo response rate was far higher in the poseltinib trial compared to the fenebrutinib trial, precluding the possibility of demonstrating a statistically significant difference between any poseltinib dose and placebo. So, in short, we do not know if targeting the BTK pathway can be effective or not.

However, to confound the issue, there was a phase II trial of fenebrutinib in SLE[18], a disease that should be more likely to respond to BTK inhibition. Patients in this study did meet the Systemic Lupus International Collaborating Clinics or revised ACR SLE criteria, had ≥ 1 serologic marker of SLE, and an SLE Disease Activity Index ≥ 6, suggesting that these patients did indeed have active SLE. Patients were required to be receiving ≥ 1 standard of care therapy but were allowed a glucocorticoid "burst" for flare rescue between Weeks 0–12 and Weeks 24–36. The primary endpoint was achieving an SLE Responder Index 4 response at Week 48. Biomarkers were assessed including the numbers of CD19+ B cells, anti-dsDNA, IgG, and a BTK-dependent RNA signature, as well as BTK occupancy. All biomarkers demonstrated inhibition of the BTK pathway with full BTK occupancy. Despite the excellent PK and PD results, the study failed, yet again for a very high placebo response. This negative study, conducted and reported at the same time as the fenebrutinib study[16], has not yet been fully published. Therefore, the results are perplexing. Did a molecule that should be more effective in SLE than RA fail because of study design issues, the lack of major importance of the BTK pathway in SLE, the ineffectiveness of targeting BTK by itself in SLE, other issues, or the placebo response? As we have not seen the full study report, it is difficult to understand why fenebrutinib was shown to be effective in RA but not SLE.

This raises a very important second question that is also highlighted by Genovese, *et al*[3]. Why such a high placebo response? This study failed not because poseltinib did not achieve a reasonable ACR20 response but because the placebo patients also achieved a reasonable ACR20 response. This has been a very problematic and disturbing trend over the past several years and has been noted in both successful and unsuccessful trials with numerous molecules in both RA and SLE[19]. The authors have explored the possible reasons for the placebo response but failed to find a satisfactory explanation. Does this occur because of the geographic location of the studies, the expertise of the investigators, allowed concomitant medications, expectation bias, or other reasons?

The answer to this question may be found if we are able to evaluate all well-designed studies conducted, particularly if the result of the study is negative. We can also learn a great deal from negative studies that are not, in retrospect, well-designed.

The more information we can see and evaluate, the clearer our understanding of clinical trial results and how to conduct them properly.

We need to see the "detours and roadblocks" so as not to go down roads that will not lead us to our goals.

REFERENCES

1. Dickersin K. The existence of publication bias and risk factors for its occurrence. JAMA 1990;263:1385-9.
2. Lee K, Bacchetti P, Sim I. Publication of clinical trials supporting successful new drug applications: a literature analysis. PLoS Med 2008;5:e191.
3. Genovese M, Spindler A, Sagawa A, Park W, Dudek A, Kivitz A, et al. Safety and efficacy of poseltinib, Bruton tyrosine kinase inhibitor, in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled, 2-part phase II study. J Rheumatol 2021;48:xxxxx.
4. Corneth O, Klein W, Hendriks R. BTK Signaling in B cell differentiation and autoimmunity. Curr Top Microbiol Immunol 2016;393:67-105.
5. Lee SK, Xing J, Catlett I, Adamczyk R, Griffies A, Liu A, et al. Safety, pharmacokinetics, and pharmacodynamics of BMS-986142, a novel reversible BTK inhibitor, in healthy participants. Eur J Clin Pharmacol 2017;73:689-98.
6. Norman P. Investigational Bruton's tyrosine kinase inhibitors for the treatment of rheumatoid arthritis. Expert Opin Investig Drugs 2016;25:891-9.
7. Smith CI, Islam TC, Mattsson PT, Mohamed AJ, Nore BF, Vihinen M. The Tec family of cytoplasmic tyrosine kinases: mammalian Btk, Bmx, Itk, Tec, Txk and homologs in other species. Bioessays 2001;23:436-46.
8. Park J, Byun J, Park J, Kim Y, Lee Y, Oh J, et al. HM71224, a novel Bruton's tyrosine kinase inhibitor, suppresses B cell and monocyte activation and ameliorates arthritis in a mouse model: a potential drug for rheumatoid arthritis of CIA. Arthritis Res Ther 2016;18:91.
9. Felson D, Anderson J, Boers M, Bombardier C, Furst D, Goldsmith C, et al; American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
10. Schafer PH, Kivitz AJ, Ma J, Korish S, Sutherland D, Li L, et al. Spebrutinib (CC-292) affects markers of B cell activation, chemotaxis, and osteoclasts in patients with rheumatoid arthritis: results from a mechanistic study. Rheumatol Ther 2020;7:101-19.
11. Goess C, Harris C, Murdock S, McCarthy R, Sampson E, Twomey R, et al. ABBV-105, a selective and irreversible inhibitor of Bruton's tyrosine kinase, is efficacious in multiple preclinical models of inflammation. Mod Rheumatol 2019;29:510-22.
12. Haselmayer P, Camps M, Liu-Bujalsk L, Nguyen N, Morandi F, Head J, et al. Efficacy and pharmacodynamic modeling of the BTK inhibitor evobrutinib in autoimmune disease models. J Immunol 2019;202:2888-906.
13. Hill RJ, Smith P, Krishnarajah J, Bradshaw JM, Masjedizadeh M, Bisconte A, et al. Discovery of PRN1008, a novel, reversible covalent BTK Inhibitor in clinical development for rheumatoid arthritis [abstract]. Arthritis Rheumatol 2015;67 Suppl 10.
14. Barf T, Covey T, Izumi R, van de Kar B, Gulrajani M, van Lith B. Acalabrutinib (ACP-196): a covalent Bruton tyrosine kinase inhibitor with a differentiated selectivity and in vivo potency profile. J Pharmacol Exp Ther 2017;363;240-52.
15. Herman AE, Chinn LW, Kotwal SG, Murray ER, Zhao R, Florero M, et al. Safety, pharmacokinetics, and pharmacodynamics in healthy volunteers treated with GDC-0853, a selective reversible Bruton's tyrosine kinase inhibitor. Clin Pharmacol Ther 2018;103:1020-8.
16. Cohen S, Tuckwell K, Katsumoto TR, Zhao R, Galanter J, Lee C, et al. Fenebrutinib versus placebo or adalimumab in rheumatoid arthritis: a randomized, double-blind, phase II trial (ANDES Study). Arthritis Rheumatol 2020;72:1435-46.
17. Crawford JJ, Johnson AR, Misner DL, Belmont LD, Castanedo G, Choy R, et al. Discovery of GDC-0853: a potent, selective, and noncovalent Bruton's tyrosine kinase inhibitor in early clinical development. J Med Chem 2018;61:2227-45.
18. Isenberg D, Furie R, Jones N, Guibord P, Galanter J, Lee C, et al. Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor, fenebrutinib (GDC-0853), in moderate to severe systemic lupus erythematosus: results of a phase 2 randomized controlled trial [abstract]. Arthritis Rheumatol 2019;71 Suppl 10.
19. Bechman K, Yates M, Norton S, Cope AP, Galloway JB. Placebo response in rheumatoid arthritis clinical trials. J Rheumatol 2020;47:28-34.