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EVALUATING DURABILITY OF RESPONSE IN NEW BIOLOGICS FOR PSORIASIS

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Introduction

Psoriasis (PsO) is a chronic inflammatory disease with a prevalence estimated at 1–3%.[1,2] Biologic therapies have revolutionized the treatment of PsO, with subsequent generations of biologics showing ever-increasing efficacy. There are currently 12 originator biologics approved in Canada. In addition, numerous biosimilars have been approved. Phase 3 trials have reported efficacy ranging from PASI 75 rates of 49% from some of the earliest biologics still available, such as etanercept, up to PASI 90 response rates of 85% for the most recent biologics such as bimekizumab.[3,4] With the number needed to treat to obtain a PASI 90 response approaching one with bimekizumab, it is important to ask how durable the response will be in order to avoid having to switch biologics after an initial response. This article will review my process for evaluating the durability of response of a new agent.

Determining Response to Biologics

An important first step is defining what is meant by a durable response. A durable response can be seen as the likelihood that the patient will have continued efficacy over time with continued therapy. Alternatively, it can be defined as the likelihood that a patient will continue therapy over time, also known as drug survival. On the surface, these concepts might seem interchangeable; however, drug survival is impacted by patients who discontinue therapy due to experiencing adverse events or other external events such as loss of insurance coverage. I generally consider drug survival a more practically useful concept, as a patient having to discontinue therapy due to an adverse event still leads to the patient having to switch therapy. As well, in clinical trials, many patients who withdraw from a trial are coded as having withdrawn consent without further explanation, making it impossible to determine if the patient withdrew due to loss of efficacy, another factor, or in some cases a combination of loss of efficacy and another factor. When I assess durability of a PsO therapy, I tend to look at the extension clinical trial, any available registry data, and my personal experience with the therapy.

I begin with personal experience, given it is the most subjective of the measures I use. The time from the start of Phase 3 trials to final approval and drug availability in Canada is typically multiple years. For example, the Phase 3 trials for bimekizumab began enrolling patients in Canada in 2017 and it was approved by Health Canada in 2022. By the time the drug became commercially available, I had been following patients for five years. I have not had any patients lose response or discontinue therapy due to adverse events. Some of the limitations of my personal experience are the limited number of patients followed and recall bias.

Regarding extension clinical trials, long-term unblinded extension studies that are primarily focused on safety typically follow Phase 3 clinical trials. The benefit of these studies is that they continue to have routine objective documentation of efficacy by trained investigators. As well, the cost of the medications in these studies usually continues to be covered for the patient, which helps remove factors such as loss of insurance coverage leading to discontinuation of the medication. However, covering the cost of the medication can also be seen as a limitation, as patients may be willing to continue on a medication they would have otherwise stopped if leaving a study means having to pay for therapy outside the context of the study.

When reviewing long-term extension studies, it is important to evaluate the inclusion criteria to enter the extension and the statistical methods used for dealing with missing data. Extension studies may limit enrollment to patients who responded in the original Phase 3 studies. Regarding statistical methods for managing missing data, studies that use observed data exclude data for patients that leave a study, even if they leave due to loss of efficacy. This leads to the appearance of higher rates of efficacy and durability than one would expect to see in clinical practice. Non-responder imputation (NRI) is the most stringent criterion, and anyone who leaves the study for any reason is considered a non-responder. In between these types of analyses are methods such as multiple imputations and modified non-responder imputation (mNRI). These methods use patient characteristics to predict what their response would have been had they not left the study. The use of the last observation carried forward method looks at the last score before a patient drops out and carries it forward; it also tends to provide results between NRI and observed data. I tend to consider NRI values when looking at durability; however, they are likely conservative compared to results observed in clinical practice, as they are most comparable between studies. If NRI is not presented, I consider the percentage of patients that discontinues the study each year as a surrogate. I generally interpret an annual loss of efficacy/drop-out rate < 10% as being reasonable and comparable to that of other biologics. Imputation methods are not consistent between studies, making it difficult to compare between studies.

Reviewing the extension studies of currently available IL17 and IL23 inhibitors, there is variability in the inclusion criteria and in the methods used to treat missing data. The guselkumab extension study includes an analysis of all patients who enrolled in the original Phase 3 study. Approximately 4% of patients lost efficacy/left the study annually between 52 weeks and 204 weeks using NRI analysis.[5] Again, approximately 4% of patients dropped out of the study annually overall. The risankizumab extension trial is ongoing and the final results have yet to be published; NRI data and the percentage of patients dropping out cannot be interpreted as not all of the patients have completed the study. While these patients are still in the study, there is missing data.[6] The tildrakizumab study only presented data separated out by initial responders and partial responders, making overall interpretation difficult for the entire group.[7] The ixekizumab extension study includes an analysis of all patients who enrolled in the original Phase 3 study, but NRI data was not published. However, approximately 8% of patients dropped out of the study annually.[8] Similarly, the secukinumab study did not present NRI data and approximately 8% of patients dropped out of the study annually.[9] The brodalumab extension study was discontinued early making it difficult to interpret due to the number of patients with missing data.[10] The bimekizumab study has data published up to week 104 for patients continuously on therapy. The published NRI data reports that 8.2% of patients lost efficacy or dropped out between week 56 and week 104.[11] In addition, there is data published up to the three-year point in patients who were PASI 90 responders at week 16. In that subgroup, approximately 5.75% of patients per year lost efficacy or dropped out between week 56 and week 148.[12]

Registry Data

Registry data tends to be the last available data for new agents, as registries include patients on commercially available drugs. Registries are limited by regional differences in government or insurance-mandated criteria for the stepwise use of biologics, and/or the ability to switch biologics, influencing how long patients remain on any given medication. Considering that bimekizumab is the newest biologic for PsO, to date there is no published registry data on drug survival. However, registry data does help clinicians understand that drug survival is not likely or only class-related. Data from the DERMIO registry shows that 23.5% and 0% of bio-naïve secukinumab- and ixekizumab-treated patients respectively discontinued therapy over 12 months of therapy.[13] Therefore, clinicians will have to await registry data for bimekizumab before extrapolating it to the other IL17 inhibitors.

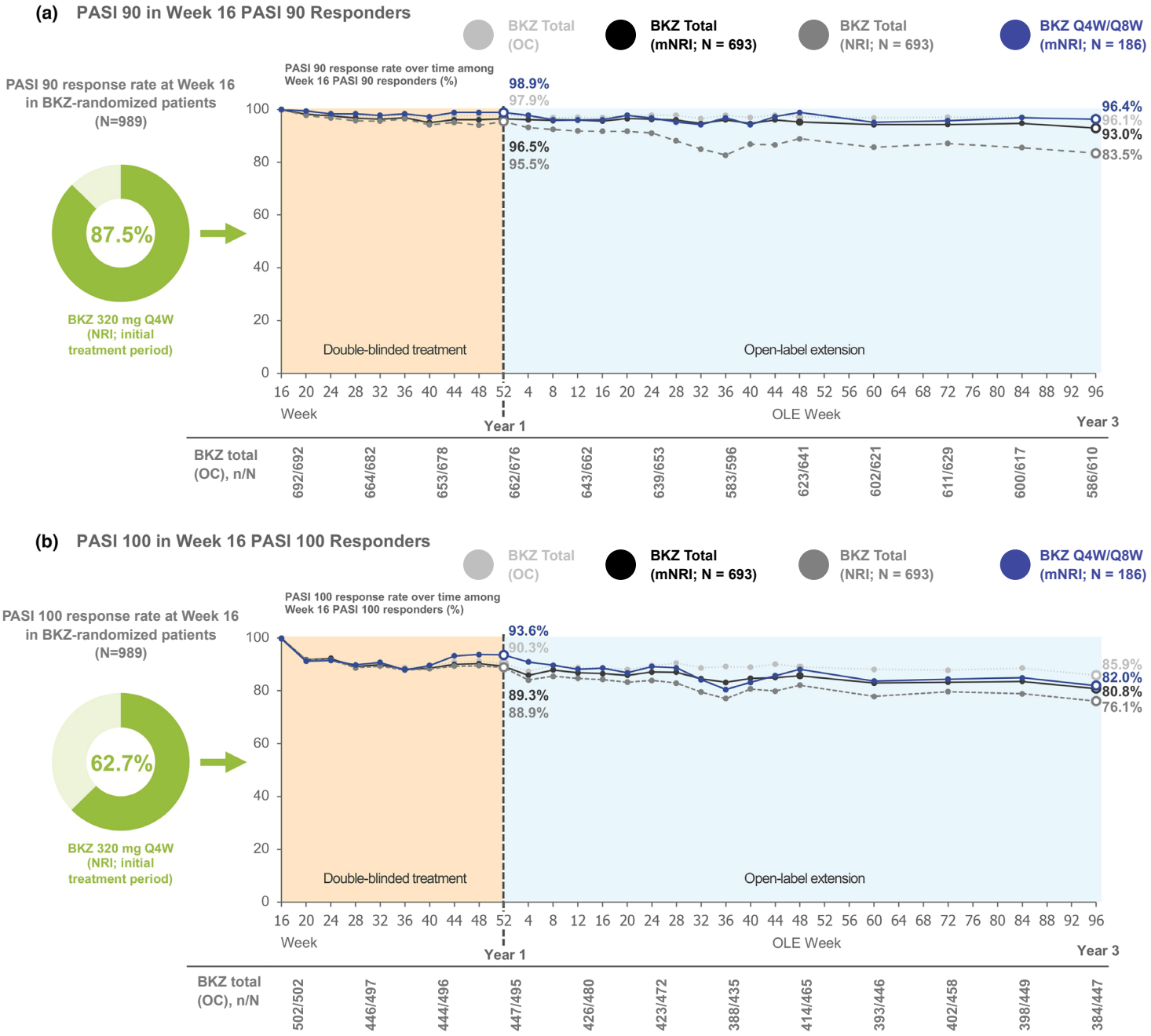

Figure 1. Maintenance of efficacy responses through 3 years in Week 16 responders: (a) PASI 90; (b) PASI 100. Week 16 responses, shown in the donut chart, are for all patients randomized to BKZ 320 mg Q4W in the initial treatment period of BE VIVID, BE READY, and BE SURE. Maintenance of response rates, shown in the kinetic plots, are for all patients who achieved the efficacy response of interest at Week 16 and received BKZ in the maintenance period and the OLE. Patients included in the Q4W/Q8W dosing group received BKZ 320 mg Q4W during the initial treatment period followed by continuous BKZ 320 mg Q8W in the maintenance period and the OLE. For mNRI analyses, patients discontinuing due to lack of efficacy or a treatment-related adverse event were counted as non-responders; multiple imputation was used for all other missing data. For NRI, patients in BE READY who entered the open-label BKZ escape arm during the randomized withdrawal period were counted as non-responders from the point of escape and throughout all of BE BRIGHT. For OC, data from the point of escape and through Week 56 of BE READY for these patients were considered as missing, and from the point of entry into BE BRIGHT their data are presented as observed; N represents the number of patients with a non-missing measurement at each timepoint, and percentages were calculated accordingly.

BKZ = bimekizumab; BSA = body surface area; mNRI = modified non-responder imputation; NRI = non-responder imputation; OC = observed case; OLE = open-label extension; PASI = Psoriasis Area and Severity Index; PASI 90/100 = ≥90/100% reduction from baseline in PASI; Q4W = every 4 weeks; Q8W = every 8 weeks. Reproduced with permission; Strober B et al.[12]

There is published durability data on bimekizumab up to three years **(Figure 1)** and there are patients who have been on therapy continuously since 2017. Overall, the durability data for bimekizumab appears favourable and consistent with that of other modern biologics for PsO.

Conclusion

Determining the durability of response to a new biologic agent in the treatment of PsO is an essential component in treating such patients as it can help prevent the need to switch biologics following the initial response. A number of subjective and objective methods are available to achieve this, including the evaluation of Phase 3 trials, extension studies and registry data as they become available.

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References

1. Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. Dermatol Clin. 1996;14:485-496.
2. Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. Arch Dermatol 2005;141:1537-1541.
3. Papp KA, Tyring S, Lahfa M, et al, Etanercept Psoriasis Study Group. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. Br J Dermatol. 2005 Jun 1;152(6):1304-1312.
4. Reich K, Papp KA, Blauvelt A, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo controlled phase 3 trial. Lancet. 2021 Feb 6;397(10273):487-498.
5. Griffiths CE, Papp KA, Song M, et al. Continuous treatment with guselkumab maintains clinical responses through 4 years in patients with moderate-to-severe psoriasis: results from VOYAGE 1. J Dermatolog Treat. 2022 Feb 17;33(2):848-856.
6. Papp KA, Lebwohl MG, Puig L. 33270 Long-term efficacy and safety of risankizumab (RZB) for the treatment of moderate to-severe plaque psoriasis: Interim analysis of results from the LIMMitless open-label extension trial beyond 4 years of follow-up. J Am Acad Dermatol. 2022 Sep 1;87(3):AB77.
7. Papp K, Reich K, Blauvelt A, et al. Clinical efficacy or tildrakizumab in patients with chronic plaque psoriasis over 2 years of treatment: results from long-term extensions to 2 phase 3 clinical studies. SKIN. 2018 Feb 23;2.
8. Blauvelt A, Lebwohl MG, Mabuchi T, et al. Long-term efficacy and safety of ixekizumab: A 5-year analysis of the UNCOVER-3 randomized controlled trial. J Am Acad Dermatol. 2021 Aug 1;85(2):360-368.
9. Langley RG, Sofen H, Dei-Cas I, et al. Secukinumab long-term efficacy and safety in psoriasis through to year 5 of treatment: results of a randomized extension of the phase III ERASURE and FIXTURE trials. Br J Dermatol. 2023 Feb 1;188(2):198-207.
10. Puig L, Lebwohl M, Bachelez H, et al. Long-term efficacy and safety of brodalumab in the treatment of psoriasis: 120-week results from the randomized, double-blind, placebo-and active comparator–controlled phase 3 AMAGINE-2 trial. J Am Acad Dermatol. 2020 Feb 1;82(2):352-359.
11. Thaçi D, Vender R, de Rie MA, et al. Safety and efficacy of bimekizumab through 2 years in patients with moderate-to-severe plaque psoriasis: longer-term results from the BE SURE randomized controlled trial and the open-label extension from the BE BRIGHT trial. Br J Dermatol. 2023 Jan 23;188(1):22-31.
12. Strober B, Tada Y, Mrowietz U, et al. Bimekizumab maintenance of response through 3 years in patients with moderate-to-severe plaque psoriasis: results from the BE BRIGHT open-label extension trial. Br J Dermatol. 2023 Jun;188(6):749-759.
13. Egeberg A, Bryld LE, Skov L. Drug survival of secukinumab and ixekizumab for moderate-to-severe plaque psoriasis. J Am Acad Dermatol. 2019 Jul 1;81(1):173-178.

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