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Assessing the Efficacy of New Biologic Therapies in Hidradenitis Suppurativa Consistency vs Bias in Outcome Measures in Moderate and Severe Disease

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Dear Editor,

Kovacs and Podda[1] present a case series of Hurley Stage 3 Hidradenitis Suppurativa patients responsive to Guselkumab (a monoclonal IL-23 antagonist) over a 12-week period as measured by the IHS4 outcome measure. A phase 2 trial of Guselkumab in HS[2] is currently underway, utilizing the HiSCR outcome measure in line with the PIONEER studies[3]. Both outcome measures have been appropriately validated both psychometrically and clinically[3,4]. HiSCR is defined as a 50% reduction in inflammatory abscess and nodule count from baseline[3]; whereas the IHS4 is a differentially weighted outcome measure, the total calculated by nodule count (weighted x1) abscess count (weighted x2) and draining fistulae count (weighted x4)[4].

Comparing results of biologic clinical trials in HS requires consistent outcome measures and acknowledgement of differences in patient characteristics, in order to draw appropriate conclusions regarding external validity. Whilst the HiSCR has the advantage of being widely used and reported in multiple RCTs, it does not consider the draining fistulae of advanced disease. This may have implications on responsiveness, particularly in the presence of low inflammatory nodule counts which can occur in highly cicatricial disease.

Disparate response rates to Adalimumab are seen in Hurley Stage 2 and Stage 3 in PIONEER data (PIONEER 1: 44.6% vs 38.6% and PIONEER 2: 62.4% vs 55.1%)[3]. It is unclear whether this is due to the low median baseline inflammatory nodule counts (PIONEER 1: 11.5 (10.92), PIONEER 2: 8.6 (6.92))[3] or inherent differences in the disease processes in stage 2 and stage 3 patients. If disease and pathogenic heterogeneity is implicated[5], this could have impacts upon the interpretation of other RCTs due to differing ratios of stage 2 and stage 3 patients[6–9] (Figure 1).

Understanding pathogenic heterogeneity in HS may lead to identification of clinical or biochemical variables which may predict clinical response to specific therapeutics. Anecdotal evidence suggests that differential response may occur between moderate (primarily inflammatory disease) and severe (fistulizing and cicatricial) disease, however

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subgroup analysis of existing trials have included cohorts too small to demonstrate statistical significance. Comparison of the efficacy rates of existing clinical trials along with the proportions of stage 2 and 3 patients are suggestive of this differential response (Figure 1).

The underlying inflammatory mechanisms differentiating Hurley Stage 2 and Stage 3 patients are proposed to involve feed-forward mechanisms of keratinocyte-derived pro-inflammatory mediators including IL-1α, IL-1β, ICAM-1 and TGF-β instigating aberrant wound healing responses, scarring and fistulae formation. The inflammatory cascade in moderate disease is more in line with the TNF-alpha and Th-17 mediated inflammatory cascade[10].

Kovacs and Podda's report[1] demonstrating response to Guselkumab in Hurley stage 3 HS supports the concept of upstream blockade of the Th17 cascade as well as leucocyte and dendritic cell mediated keratinocyte/fibroblast stimulation in advanced disease[10], however in the absence of HiSCR and RCT data it is difficult to determine where Guselkumab may fit upon the efficacy spectrum in HS. Whilst HiSCR is the accepted primary outcome measure for clinical trials in HS for the forseeable future, the IHS4 has a complementary role, particularly in the assessment of advanced disease where the HiSCR may suffer from decreased responsiveness.

The open reporting and availability of de-identified individual patient data from randomized clinical trials of new biologic agents in HS may allow for the retrospective collation of IHS4 and HiSCR statistics to allow direct comparison between studies. This would provide the greatest utility in determining the cause of variation in response rates to biologic therapies in advanced HS, whether this be a product of the outcome measure used, or a possible signal of disease heterogeneity.

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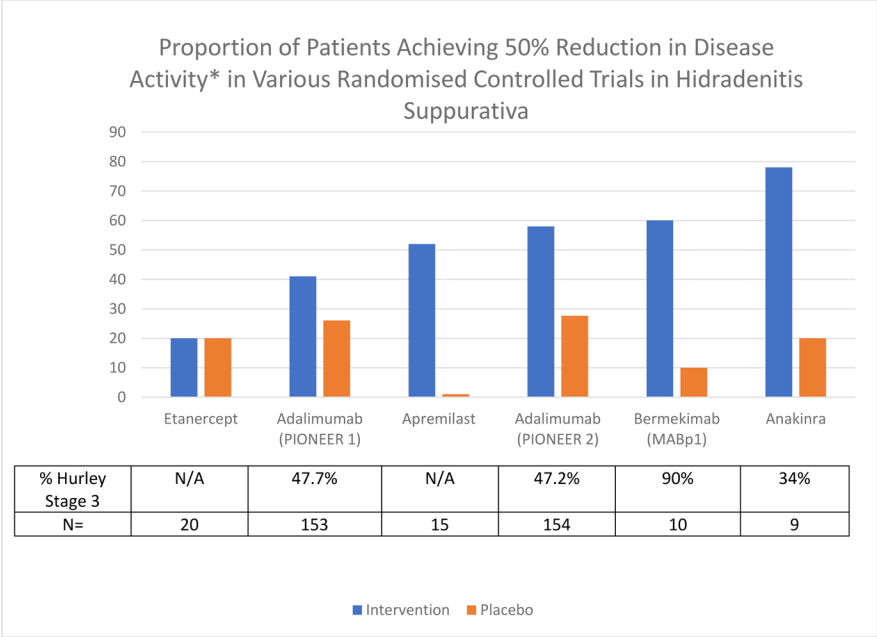

% Hurley Stage 3	N/A	47.7%	N/A	47.2%	90%	34%
N=	20	153	15	154	10	9

Figure 1:

Graphical representation of proportion of patients achieving HiSCR (50% reduction of inflammatory nodules and abscesses at Week 12 compared to Baseline) in various RCTs in Hidradenitis Suppurativa – Intervention Group versus Placebo.

(NB: Apremilast Study results are from Week 16, all other results from Week 12.)

*50% reduction in disease activity defined by HiSCR or calculated based upon raw data of abscess and nodule count.