Ability of the GARD®skin assay to Predict Skin Sensitization Response in the Guinea Pig Maximization Test

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Abstract ID#3468

Conclusions

- The GARD®skin assay is able to predict skin sensitization potential in humans with a level of accuracy that is equal to or exceeds that of GPMT and the LLNA.
- As a result, the GARDskin assay serves as a promising alternative to assess the skin sensitization potential of medical devices.

Introduction

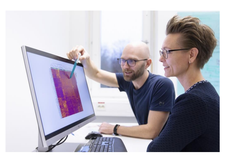
The preclinical safety assessment of medical devices typically involves an evaluation of the skin sensitization potential of the device. The GARDskin assay is being proposed as an in vitro alternative to the animal-based tests, Guinea Pig Maximization Test (GPMT) and the Local Lymph Node Assay (LLNA), that are commonly used to assess the skin sensitization potential of medical devices. The ability of the GARDskin assay to replace LLNA for prediction of skin sensitization response has been evaluated [2,3,4] but since GARDskin also is proposed as an alternative to the GPMT, we have evaluated the concordance of the prediction of the GARDskin assay with the in vivo response obtained in both of the animal-based tests.

Methods

The ability of the GARDskin assay to predict the skin sensitizing potential of 122 compounds was assessed by comparing the results from this test method to results obtained in the animal-based tests, LLNA and GPMT. The correlation to the human skin sensitizing potential of these compounds was also evaluated. The step-wise procedure for conducting the GARDskin assay is illustrated in **Figure 1.** For more detailed information see Johansson et al 2019 [2].

Step 1
Expose Cells (SenzaCell™) to the test sample at determined concentration.

Step 2
Measure the gene expression levels of 200 biomarkers, the genomic biomarker signature.



Step 3
GARD Data Analysis Application makes a binary prediction based on gene expression analysis.

Figure 1: The GARDskin assay in three steps

The results of the GARDskin assay were provided by SenzaGen. The data for the GPMT and the LLNA were largely obtained from the ICCVAM (2011) report [1], from the available ECHA REACH dossiers [5], and from the open literature. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of each of the test methods for a specific set of compounds was assessed using the online MedCalc calculator.

Results and Discussion

Based on the results of the GARDskin assay for 122 compounds, this in vitro assay shows a high concordance with the results of the LLNA (87.5%); however, the concordance with results obtained in the GPMT is much lower (71.2%), as shown in Table 1 below.

The relatively poor concordance of results from the GARDskin assay and the GPMT is largely due to the relatively high number of False Positive (FP) results (15 out of 73) that occur compared to the number of FPs seen in the GARDskin vs. LLNA comparison (2 out of 80). The high number of FP in the GARDskin vs. GPMT comparison results from the inaccurate characterization of the human skin sensitization potential of these compounds by the GPMT. Therefore, the low concordance between the GARDskin assay and the GPMT is primarily due to inaccurate predictions of human skin sensitization potential by the GPMT and not because of shortcomings of the GARDskin assay.

Table 1: Statistical evaluation of the ability of the GARDskin assay to predict response in animal-based skin sensitivity assays (GPMT and the LLNA)

	GARDskin vs. GPMT	GARDskin vs. LLNA
Accuracy (%)	71.2	87.5
Sensitivity (%)	86.7	87.5
Specificity (%)	46.4	87.5
Positive Predictive Value (%)	72.2	96.6
Negative Predictive Value (%)	68.4	63.6

Further, as shown in Table 2, the GARDskin assay (88.7% accuracy) outperforms the GPMT (83.0% accuracy) in the ability to predict the human sensitization response of compounds in this dataset, where the predictive ability of the GARDskin assay and the animal-based skin sensitization tests is compared to the human skin sensitization potential of these compounds. The GARDskin assay also shows a good correlation between sensitivity and specificity, meaning that it has a good balance between false negative and false positive results.

Table 2: Statistical comparison of the ability of GARDskin, LLNA, and GPMT to predict human skin sensitization response

	GARDskin vs. Human	GPMT vs. Human	LLNA vs. Human
Accuracy (%)	88.7	83.0	94.0
Sensitivity (%)	89.7	79.1	97.6
Specificity (%)	84.6	100.0	75.0

In summary, the GARDskin assay is able to predict the results of the LLNA with a higher degree of accuracy than predictions of results from the GPMT; however as mentioned before this discrepancy is due to a high number of false positive (FP) results obtained when GARDskin results are compared to those obtained in the GPMT. The miscategorization of these compounds as FP is not actually "false" in terms of predicting the correct sensitization response, because the GARDskin test is able to successfully predict the human skin sensitization potential of essentially all of the compounds with a FP in the GARDskin vs. GPMT comparison. Also, the ability of the GARDskin assay to predict the human skin sensitization response of these compounds is comparable to that of the LLNA and both of these tests are superior to the GPMT in predicting the human sensitization response of this set of compounds.

The results of this project show that the GARDskin assay is able to predict skin sensitization potential with a level of accuracy that is equal to or exceeds that of the currently accepted animal-based tests, suggesting that the GARDskin assay can serve as a promising alternative to the GPMT and the LLNA as a means to assess the skin sensitization potential of medical devices.

References:

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