Early Identification of Steroid Resistant Acute Graft-Versus-Host Disease Patients following Stem Cell Transplant

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Abstract

Background: For many patients with high-risk cancers, allogeneic stem cell transplant (SCT) is the only curative option. A major risk of SCT is acute graft versus host disease (aGVHD). About 50% of SCT patients develop aGVHD as a part of their course. Glucocorticoids are the mainstay of therapy in aGVHD patients. Of the patients that develop aGVHD, about 50% develop a steroid refractory/resistant form. These patients tend to require higher doses of steroids and many will require additional medications to manage them appropriately. Identifying these patients early is important in order to optimize treatment and avoid transplant related morbidity and mortality. Although there have been biomarkers to help identify these patients, they have not been optimal. Therefore, there have been no validated prognostic tests to identify these patients. Also, there have not been studies to examine whether host factors play a role in influencing the steroid sensitivity of SCT patients. Therefore, there is a need for a prognostic test to identify these patients and study these factors. We have used a Fluorescein labeled dexamethasone (F-Dex)monocyte binding assay to study glucocorticoid sensitivity in other patients populations. We propose to use this assay to identify and study this aGVHD subset.

Objectives: To study the steroid sensitivity of recipients and their related donors prior to SCT using a Fluorescein labeled dexamethasone (F-Dex) monocyte binding assay to help identify potential aGVHD patients with steroid resistance. To use the F-Dex assay to analyze SCT patients at the time of the development of aGVHD in order to determine whether host cell factors can influence the glucocorticoid sensitivity of SCT patients and cause steroid resistant aGVHD.

Methods: Collection blood samples from 90 recipient/donor pairs 30 days prior to the SCT and at the time of the development of aGVHD. The samples will be analyzed using a Fluorescein labeled dexamethasone (FDEX) monocyte binding assay.

Results: Currently preliminary results are being ascertained.

Conclusion: Our hope is that the use of the F-Dex binding assay will help in the early identification of steroid refractory/resistant aGVHD patients, as well as to study whether host cell factors influence steroid sensitivity. This study can allow identified steroid refractory/resistant aGVHD patients to be treated appropriately, avoiding transplant related morbidity and mortality and help to elucidate factors that may cause their steroid resistance.

Objectives

- To study the steroid sensitivity of recipients and their related donors prior to SCT using a Fluorescein labeled dexamethasone (F-Dex) monocyte binding assay to help identify potential aGVHD patients with steroid resistance.
- To use the F-Dex assay to analyze SCT patients at the time of the development of aGVHD in order to determine whether host cell factors can influence the glucocorticoid sensitivity of SCT patients and cause steroid resistant aGVHD.

Methods

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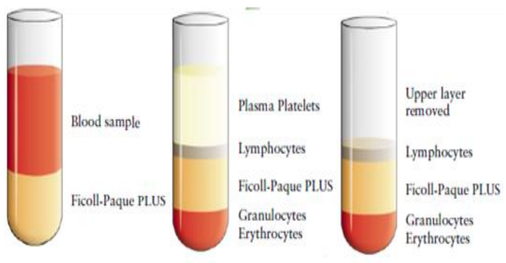
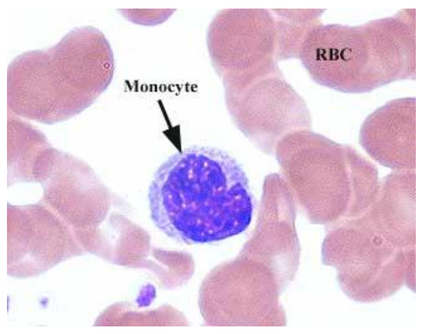
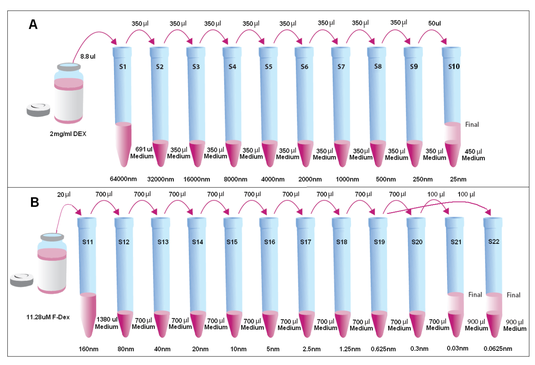
- The samples will be analyzed using a Fluorescein labeled dexamethasone (FDEX) monocyte binding assay.

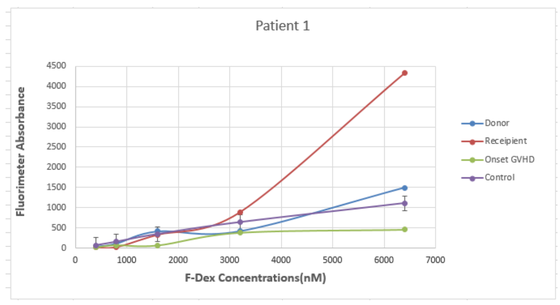


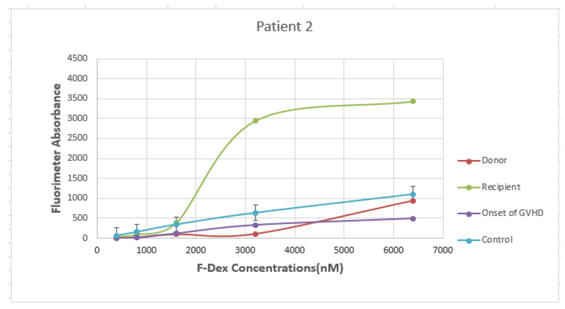


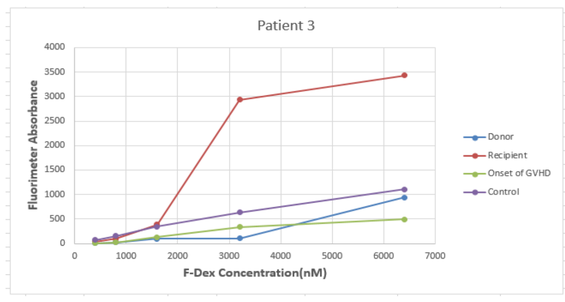


Results

- Initial patients analyzed using the F-Dex monocyte binding assay were not shown to be steroid resistant and did not have steroid resistant GVHD clinically
- Did note that recipient F-Dex data was similar to that of the donor after transplant

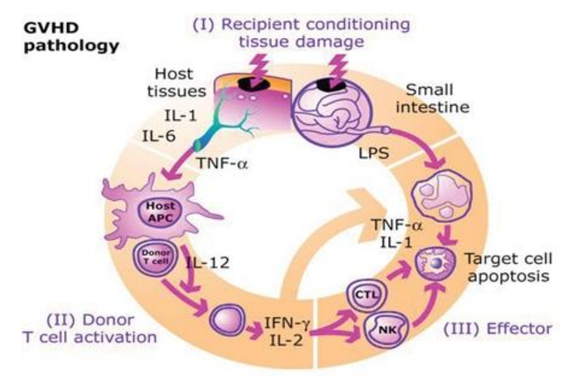


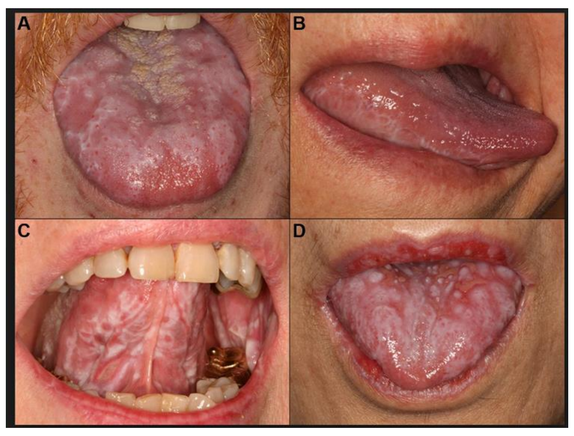


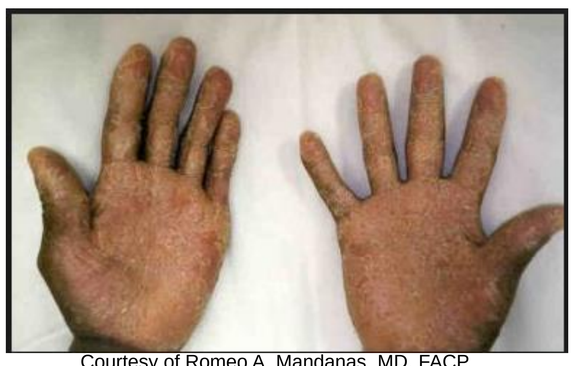


Background

For many patients with high-risk cancers, allogeneic stem cell transplant (SCT) is the only curative option. A major risk of SCT is acute graft versus host disease (aGVHD). About 50% of SCT patients develop aGVHD as a part of their course. Glucocorticoids are the mainstay of therapy in aGVHD patients. Of the patients that develop aGVHD, about 50% develop a steroid refractory/resistant form. These patients tend to require higher doses of steroids and many will require additional medications to manage them appropriately. Identifying these patients early is important in order to optimize treatment and avoid transplant related morbidity and mortality. Although there have been biomarkers to help identify these patients, they have not been optimal. Therefore, there have been no validated prognostic tests to identify these patients. Also, there have not been studies to examine whether host factors play a role in influencing the steroid sensitivity of SCT patients. Therefore, there is a need for a prognostic test to identify these patients and study these factors. We have used a Fluorescein labeled dexamethasone (F-Dex)monocyte binding assay to study glucocorticoid sensitivity in other patients populations. We propose to use this assay to identify and study this aGVHD subset.







Courtesy of Romeo A. Mandanas, MD, FACP.

Conclusion

The F-Dex binding assay has been a good predictor of clinical outcome thus far, but this is only based on initial patients. Our hope is that the use of the F-Dex binding assay on additional patients will help in the early identification of steroid refractory/resistant aGVHD patients, as well as to study whether host cell factors influence steroid sensitivity.. With the analysis of additional patients, this study can allow identified steroid refractory/resistant aGVHD patients to be treated appropriately, avoiding transplant related morbidity and mortality and help to elucidate factors that may cause their steroid resistance.

References

Bray PJ, Cotton RG. Variations of the human glucocorticoid receptor gene (NR3C1): pathological and in vitro mutations and polymorphisms. *Hum Mutat.* Jun 2003;21(6):557-568.

M Berger, E Biasin, F Saglio and F Fagioli· Innovative approaches to treat steroid-resistant or steroid refractory GVHD. *Bone Marrow Transplantation* (2008) 42, S101–S105; doi:10.1038/bmt.2008.294

Nathaniel Treister, Christine Duncan, Corey Cutler, Leslie Lehmann. How we treat oral chronic graft-versus-host diseaseBlood 2012 120:3407-3418; doi:10.1182/blood-2012-05-393389
Reddy, P. and Ferrara, J.L.M., Mouse models of graft-versus-host disease (February 28, 2009), StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.36.1

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Adrenals and HPA Axis

Steven Ghanny

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