UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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DECLARATION OF JAMES L. MULLINS, Ph.D.

Mail Stop PATENT BOARD
Patent Trial and Appeal Board
U.S. Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

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I, James L. Mullins, hereby declare under penalty of perjury:

I. INTRODUCTION

1. I have personal knowledge of the facts and opinions set forth in this declaration, I believe them to be true, and if called upon to do so, I would testify competently to them. I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both.

2. I am a retired academic librarian working as the Founder and Owner of the firm Prior Art Documentation Librarian Services, LLC at 106 Berrow, Williamsburg, VA 23188. Attached as Appendix A is a true and correct copy of my Curriculum Vitae describing my background and experience. Further information about my firm, Prior Art Documentation Librarian Services, LLC (PADLS), is available at www.priorartdoclib.com.

3. I have been retained by Baker Botts LLP to investigate the authenticity and dates of public accessibility of certain documents for use in one or more *inter partes* review proceedings. For this service, I am being paid my usual hourly fee of $185/hour. My compensation in no way depends on the substance of my testimony or the outcome of the proceeding.

II. BACKGROUND AND QUALIFICATIONS

4. I am presently Dean of Libraries Emeritus and Esther Ellis Norton Professor Emeritus, Purdue University, 2018 – present. Other experience includes:

- Dean of Libraries and Professor & Esther Ellis Norton Professor, Purdue University, West Lafayette, IN, 2004-2017.

- Assistant/Associate Director for Administration, Massachusetts Institute of Technology (MIT), Cambridge, MA, 2000-2004.

- University Librarian and Director, Falvey Memorial Library, Villanova University, Villanova, PA, 1996-2000

- Director of Library Services, Indiana University South Bend, South Bend, IN, 1978-1996. Part-time instructor, School of Library and Information Science, Indiana University, Bloomington, IN, 1978 -1996.

- Associate Law Librarian, and associated titles, Indiana University School of Law, Bloomington, IN, 1974-1978

- Catalog Librarian, Assistant Professor, Georgia Southern College (now University), Statesboro, GA, 1973-1974.

5. Over the course of my career as a librarian, instructor of library science, author of scholarly publications, and presenter at national and international conferences, I have had experience with catalog records and online library management systems built around Machine-Readable Cataloging (MARC) standards.

6. In the course of more than forty-four years as an academic librarian and scholar, I have been an active researcher. In my years as a librarian, I have facilitated the research of faculty colleagues either directly or through the provision of and access to the requisite print and/or digital materials and services at the universities where I worked. I have kept current on the professional library science literature and

served on the editorial board of the most prominent library journal, *College and Research Libraries*. This followed service as the chair of the Research Committee of the Association of College and Research Libraries (ACRL), a division of the American Library Association (ALA). As an academic library administrator, I have had responsibility to ensure that students were educated to identify, locate, assess and integrate information garnered from library resources.

III. PRELIMINARIES

7. I am not a lawyer, and I am not rendering an opinion on the legal question of whether a particular document is, or is not, a "printed publication" under the law.

8. I am, however, rendering my expert opinion on the authenticity of the documents referenced herein and on when and how these documents were disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, could have located the documents by November 6, 2001.

9. I am informed by counsel that an item is considered authentic if there is sufficient evidence to support a finding that the item is what it is claimed to be. I am also informed that authenticity can be established based on the contents of the documents themselves, such as the appearance, content, substance, internal patterns,

or other distinctive characteristics of the item, taken together with all of the circumstances.

10. I am informed by counsel that a reference qualifies as a "printed publication" if it was sufficiently accessible to the public interested in the art. I am also informed that dissemination and public accessibility are the keys in determining whether a reference was "published." I understand that a given reference is publicly accessible upon a satisfactory showing that such a document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence can locate it. I have also been informed by counsel that materials available in a library constitute printed publications if they are cataloged and indexed according to general library practices that make the references available to members of the interested public, and that evidence relevant to this inquiry includes the acquisition, indexing, cataloging, shelving, and circulation practices of the library.

A. Materials considered

11. In forming the opinions expressed in this declaration I have reviewed the documents and appendices referenced herein. These materials were records created in the ordinary course of business by publishers, libraries, indexing services, and others. From my years of experience, I am familiar with the process for creating many of these records, and I know that these records are created by people with

knowledge of the information in the record. Further, these records are created with the expectation that researchers and other members of the public will use them. All materials cited in this declaration and its appendices are of a type that experts in my field would reasonably rely upon and refer to in forming their opinions.

B. Persons of ordinary skill in the art

12. I am told by counsel that the subject matter of this proceeding relates to methods of treating multiple myeloma by administering lenalidomide and dexamethasone on a 28-day cycle that includes a seven-day rest period.

13. I have been informed by counsel that a "person of ordinary skill in the art at the time of the invention" is a hypothetical person who is presumed to be familiar with the relevant field and its literature at the time of the invention. This hypothetical person is also a person of ordinary creativity, capable of understanding the scientific principles applicable to the pertinent field.

14. I am told by counsel that a person of ordinary skill in this subject matter or art would have had several years of experience as a practicing physician in the fields of oncology and hematology. Such a person also would have had experience with the administration of therapeutic agents and the development of drug regimens and dosing schedules. Typically, such a person would have an M.D. as well as experience in clinical oncology or pharmacology.

15. In the early 2000s such a person would have had access to a vast array of print resources in methods of treating multiple myeloma, access to reference librarians (e.g., at universities), and access to a fast-changing set of online resources.

C. Library catalog records

16. Some background on MARC formatted records, OCLC, and WorldCat is helpful to understand the library catalog records discussed in this declaration. MARC practices have been consistent since the MARC format was developed by the Library of Congress in the 1960s and, by the early 1970s, became the U.S. national standard for disseminating bibliographic data. By the mid-1970s, MARC format became the international standard and persists through the present. The MARC practices discussed below were in place during the late 1990s and early 2000s timeframe relevant to the documents referenced herein.

17. Libraries world-wide have used the machine-readable MARC (Machine-Readable Cataloging) format for catalog records. MARC formatted records have provided a variety of subject access points based on the content of the document being cataloged. Subject headings may be found in the MARC fields 6XX. For example, MARC Field 600 identifies personal names used as subjects and the MARC Field 650 identifies topical terms. A researcher might discover material relevant to his or her topic by a search using the terms employed in the MARC Fields 6XX.

18. The MARC Field 040, subfield "a," identifies the library or other entity that created the original catalog record for a given document and transcribed it into machine readable form. The MARC Field 008 identifies the date when this first catalog record was entered on the file. This date persists in subsequent uses of the first catalog record, although newly-created records for the same document, separate from the original record will show a new date. It is not unusual to find multiple catalog records for the same document

19. WorldCat is the world's largest public online catalog, maintained by the Online Computer Library Center, Inc., or OCLC, and built with the records created by the thousands of libraries that are members of OCLC. OCLC has provided bibliographic and abstract information to the public based on MARC records, and WorldCat has provided a user-friendly interface for the materials maintained by OCLC. WorldCat requires no knowledge of MARC tags and codes and does not require a log-in or password. WorldCat is easily accessible through the World Wide Web to all who wish to search it; there are no restrictions to be a member of a particular community, etc. The date a given catalog record was created (corresponding to the MARC Field 008) appears in some detailed WorldCat records as the Date of Entry but not necessarily all. Although WorldCat is a more modern system, libraries had access to the OCLC database since the mid-1980s, and well before 1999.

20. Once the MARC record is created by a cataloger at an OCLC participating member institution, it becomes available to other OCLC participating members through OCLC databases such as WorldCat, where persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it.

D. Periodical publications

21. A library typically creates a catalog record for a periodical publication when the library receives its first issue. When the institution receives subsequent issues/volumes of the periodical, the issues/volumes are checked in (often using a date stamp), added to the institution's holding records, and made available very soon thereafter – normally within a few days of receipt or (at most) within a few weeks of receipt.

22. The initial periodicals record will sometimes not reflect all subsequent changes in publication details (including minor variations in title, frequency, etc.,).

E. Ownership and date stamp

23. Every library has a different practice or policy on whether-or-not to date stamp, but all will have an ownership stamp somewhere in the book. The ownership stamp typically appears on the cover page, verso of the cover page, or a designated page within the book, sometimes even on the top, side, or bottom edge of the monograph or periodical. The ownership and date stamp can also vary from one

library to another when the stamp is entered on the monograph or periodical. It could occur when received in acquisitions after shipment to the library, or it could be at time of cataloging.

F. Indexing

24. A researcher may discover material relevant to his or her topic in a variety of ways. One common means of discovery is to search for relevant information in an index of periodical and other publications. Having found relevant material, the researcher will then normally obtain it online, look for it in libraries, or purchase it from the publisher, a bookstore, a document delivery service, or other provider. Sometimes, the date of a document's public accessibility will involve both indexing and library date information. Date information for indexing entries is, however, often unavailable. This is especially true for online indices.

25. Indexing services use a wide variety of controlled vocabularies to provide subject access and other means of discovering the content of documents. The formats in which these access terms are presented vary from service to service.

26. Online indexing services commonly provide bibliographic information, abstracts, and full-text copies of the indexed publications, along with a list of the documents cited in the indexed publication. These services also often provide lists of publications that cite a given document. A citation of a document is evidence that

the document was publicly available and in use by researchers no later than the publication date of the citing document.

27. ***Medline*** – This is a database of bibliographic information from the National Library of Medicine. The database provides access to publications in the life sciences and to biomedical information from all areas of medicine and health care. More than 26 million records are included in the database. These have been indexed from some 5,639 publications issued from 1950 to the present. The database is freely available via the PubMed interface. One of the most heavily used medical databases, Medline had over 1.5 billion users in 2011.

28. ***Web of Science*** – As its print predecessors, *Science Citation Index*, *Social Science Citation Index* and *Arts and Humanities Citation Index*, this database is the starting point for researchers and librarians because of the very thorough coverage. The database includes the content of the print index with 100 years of back files and extremely broad coverage, including over 250 subject categories. Web of Science indexes 1,700 arts and humanities journals from 1975 to the present, 8,500 scientific journals from 1900 to the present, and some 300 social science journals also covering 1900 to the present. It is used by more than 6,000 scholarly institutions worldwide.

29. ***Google Scholar*** – This web search engine indexes full text or metadata of scholarly literature, covering numerous formats and disciplines. The size of the

database is not published by Google, but researchers have estimated that it contained approximately 160 million items in 2014. (see Oduna-Malea, Enrique, Ayllon, Juan Manuel, Martin-Martin, Alberto, Delgado Lopez-Cozar, Emilio "About the size of Google Scholar: playing the numbers", Sep. 2015, Scientometrics, 104(3), pp. 931-949, https://arxiv.org/ftp/arxiv/papers/1407/1407.6239.pdf. The database is not limited by type of publication and includes dissertations, prepublication materials, technical reports, patents and more. Google Scholar is similar to many subscription databases, e.g., Scopus and Web of Science, in its broad subject coverage.

IV. OPINION REGARDING INDIVIDUAL DOCUMENTS

A. Palumbo, A., et al., "Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma," Haemtologica, Volume 86, Number 4 (April 2001): 399-403. (Palumbo)

1. *Authentication*

30. "Palumbo" refers to a research paper by A. Palumbo, et al., published in the journal Haemtologica, volume 86, number 4 (April 2001), pages 399-403. I requested a copy of the Palumbo paper from the Wisconsin Tech Services (WTS) which provided scans from a print copy held in the National Library of Medicine located in Bethesda, Maryland.

31. Exhibit A1 is a true and accurate copy of the cover, title page, publisher information, table of contents and the Palumbo paper from the print issue of Haemtologica, volume 86, number 4 (April 2001). On the cover of the issue is the

ownership and date label (upper left-hand corner) of the National Library of Medicine, that shows a check-in date of 2001-05-22 (May 22, 2001).

32. Exhibit A1 is a true and accurate copy of the Palumbo paper from the print copy owned by the National Library of Medicine. The copy of the Palumbo paper in Exhibit A1 is not missing any intermediate pages of the article's text, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document. Exhibit A1 was found within the custody of a library – a place where, if authentic, it would likely be housed and available.

33. The Palumbo paper is also readily available online. Exhibit A2 is a true and accurate copy of the Palumbo paper that I downloaded at the Haemtologica website at: http://www.haematologica.org/content/86/4/399.full.pdf+html on August 17, 2018 – a place where, if authentic, the Palumbo paper would likely be found and made available. Based on my review, the text and figures of Exhibit A2 are the same as Exhibit A1. Exhibit A2 was filed as Exhibit 1015 in this proceeding.

34. I conclude, based on finding the Palumbo paper in print, in both a library and online through a reputable, disciplinary database, that the Palumbo paper is an authentic document and that Exhibit A1 and Exhibit A2 (Exhibit 1015) are authentic copies of the Palumbo paper.

2. *Public Accessibility*

35. Exhibit A3 is a true and accurate copy of the record in OCLC WorldCat for Haematologica. The OCLC WorldCat record indicates that Haematologica was cataloged as a periodical in 1920. WorldCat shows 81 libraries world-wide holding the journal Haematologica among those 81 is the National Library of Medicine. Exhibit A3 indicates that Haematologica was cataloged and indexed in a meaningful way—including by title and by subject, including Hematology -- Periodicals; Blood -- Diseases -- Periodicals; and Blood -- Periodicals.

36. Exhibit A4 is the OPAC (online catalog) and MARC records for Haematologica from the National Library of Medicine (NLM). The NLM OPAC record indicates that the library has held this title in print from its start in 1920. Frequency changed in 1998 when the journal became monthly and has continued with that frequency.

37. Allowing for a week at the most between the date stamp, May 22, 2001, and the issue's availability on the shelf, it would have been available no later than the end of May 2001.

38. Exhibit A5 is further evidence that the Palumbo paper was publicly available no later than November 1, 2001. The Palumbo paper is cited as number 24 in References on page 587 of the article by Bernard Combe, entitled "Thalidomide: new indications?" published in Joint Bone Spine, volume 68 (2001), pages 582-587

in December 2001. Because it takes at least six months for a manuscript such as this to reach the publication stage, the Palumbo paper would have had to have been publicly available by no later than November 1, 2001.

3. *Conclusion*

39. Based on the evidence presented here—publication in a widely held journal, online indexing and publication, and library processing—it is my opinion that the Palumbo paper (attached as Exhibit A1 and Exhibit A2 (Exhibit 1015)) is an authentic document. It is also my opinion that the Palumbo paper was publicly available to researchers no later than the end of May 2001. Thus, in my opinion, the Palumbo paper was sufficiently accessible to the public interested in the art, such that an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of the Palumbo paper in the journal Haematologica no later than the end of May 2001.

B. Muller, G.W., et al., "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production," Bioorganic and Medicinal Chemistry Letters. Volume 9, Number 11 (June 7, 1999): 1625-30. (Muller)

1. *Authentication*

40. "Muller" refers to a research paper by G.W. Muller, et. al., published in the journal Bioorganic and Medicinal Chemistry Letters, volume 9, number 11 (June 7, 1999), pages 1625-30. I requested a copy of the Muller paper from the Wisconsin

Tech Services (WTS) which provided scans from a print copy held in the Linda Hall Library located in Kansas City, Missouri.

41. Exhibit B1 is a true and accurate copy of the cover, title page, publisher information, title page, table of contents and the Muller paper from the print issue of Bioorganic and Medicinal Chemistry Letters, volume 9, number 11 (June 7, 1999), pages 1625-30. On the cover of the issue and the title page is the ownership and date stamp of the Linda Hall Library that shows a check-in date of June 16, 1999.

42. Exhibit B1 is a true and accurate copy of the Muller paper from the print copy owned by the Linda Hall Library. The copy of the Muller paper in Exhibit B1 is not missing any intermediate pages of the article's text, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document. Exhibit B1 was found within the custody of a library – a place where, if authentic, it would likely be housed and available.

43. The Muller paper is also readily available online. Exhibit B2 is a true and accurate copy of the Muller paper that I downloaded through the Science Direct database accessed by Purdue University Libraries: https://ac-els-cdn-com.ezproxy.lib.purdue.edu/S0960894X99002504/1-s2.0-S0960894X99002504-main.pdf?tid=f432a813-e295-45c0-a0ac-caaf804e3d88&acdnat=15345289500a27ce19bb05b9d5f04970e260d102a7 on August 17, 2018 – a place where, if authentic, the Muller paper would likely be found and made available. Based on my review, the text and figures

of Exhibit B2 are the same as Exhibit B1. Exhibit B2 was filed as Exhibit 1008 in this proceeding.

44. I conclude, based on finding the Muller paper in print, in both a library and online through a reputable, disciplinary database, that the Muller paper is an authentic document and that Exhibit B1 and Exhibit B2 (Exhibit 1008) are authentic copies of the Muller paper.

2. *Public Accessibility*

45. Exhibit B3 is a true and accurate copy of the record in OCLC WorldCat for Bioorganic and Medicinal Chemistry Letters. The OCLC WorldCat record indicates that Bioorganic and Medicinal Chemistry Letters was cataloged as a periodical in 1991. WorldCat shows 779 libraries world-wide holding the journal Bioorganic and Medicinal Chemistry Letters. Exhibit B3 indicates that Bioorganic and Medicinal Chemistry Letters was cataloged and indexed in a meaningful way—including by title and by subject, including Bioorganic chemistry -- Periodicals; Pharmacological chemistry -- Periodicals; Biochemistry -- Periodicals.

46. Exhibit B4 is the OPAC (online catalog) and MARC records for Bioorganic and Medicinal Chemistry Letters from the Linda Hall Library. The Linda Hall Library OPAC record indicates that the library has held this title in print from its start in 1991, received as a monthly issue.

47. Allowing for a week at the most between the date stamp, June 16, 1999, and the issue's availability on the shelf, it would have been available no later than the end of June 1999.

48. Exhibit B5 is further evidence that the Muller paper was publicly available in 1999. The Muller paper is cited as number 40 in References on page 1112 of the article by Laura C. Corral and Gilla Kaplan, entitled "Immunomodulation by Thalidomide and Thalidomide Analogues?" published in Annals of Rheumatic Diseases, 1999:58 (Suppl), pages 1107-1113, received by the National Library of Medicine in December 1999, as discussed in Exhibit E1 below.

3. *Conclusion*

49. Based on the evidence presented here—publication in a widely held journal, online indexing and publication, and library processing—it is my opinion that the Muller paper (attached as Exhibit B1 and Exhibit B2 (Exhibit 1008)) is an authentic document. It is also my opinion that the Muller paper was publicly available to researchers at least by the end of June 1999. Thus, in my opinion, the Muller paper was sufficiently accessible to the public interested in the art, such that an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of the Muller article in the journal Bioorganic and Medicinal Chemistry Letters no later than the end of June 1999.

C. Hideshima, T., et al., "Thalidomide and its analogs overcome drug resistance of human multiple myleloma cells to conventional therapy," Blood, Volume 96, Number 9 (November 1, 2000): 2943-50. (Hideshima)

1. *Authentication*

50. "Hideshima" refers to a research paper by T. Hidshima, et al., "Thalidomide and its Analogs Overcome Drug Resistance of Human Multiple Myleloma Cells to Conventional Therapy" in Blood, volume 96, number 9 (November 1, 2000), pages 2943-2950. I requested a copy of the Hideshima paper from the Wisconsin Tech Services (WTS) which provided scans from a print copy held in the National Library of Medicine located in Bethesda, Maryland.

51. Exhibit C1 is a true and accurate copy of the cover, title page, table of contents and the Hideshima paper from the print issue of the journal Blood, volume 96, number 9 (November 1, 2000), pages 2943-2950. On the cover of the issue is the ownership label of the National Library of Medicine that shows that this issue of Blood was received and checked-in November 9, 2000.

52. Exhibit C1 is a true and accurate copy of the Hideshima paper from the print copy owned by the National Library of Medicine. The copy of the Hideshima paper in Exhibit C1 is not missing any intermediate pages of the article's text, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document. Exhibit C1 was found within the custody of a library – a place where, if authentic, it would likely be housed and available.

53. The Hideshima is also readily available online. Exhibit C2 is a true and accurate copy of the Hideshima paper that I downloaded through the journal Blood website: http://www.bloodjournal.org/content/bloodjournal/96/9/2943.full.pdf on August 28, 2018 – a place where, if authentic, the Hideshima paper would likely be found and made available. Based on my review, the text and figures of Exhibit C2 are the same as Exhibit C1. Exhibit C2 was filed as Exhibit 1016 in this proceeding.

54. I conclude, based on finding the Hideshima paper in print, in both a library and online through a reputable, disciplinary database, that the Hideshima paper is an authentic document and that Exhibit C1 and Exhibit C2 (Exhibit 1016) are authentic copies of the Hideshima paper.

2. *Public Accessibility*

55. Exhibit C3 is a true and accurate copy of the record in OCLC WorldCat for the journal Blood. The OCLC WorldCat record indicates that the journal Blood is held in 838 libraries world-wide including the National Library of Medicine. Exhibit C3 indicates that the journal Blood was cataloged and indexed in a meaningful way—including by title and by subject, including: Blood -- Periodicals; Hematology -- Periodicals; and Blood.

56. Exhibit C4 is the OPAC (online catalog) and Exhibit C5 is the MARC records for the journal Blood from the National Library of Medicine. The National Library of Medicine OPAC record indicates that the library has held this title in print

from its start in 1946. Exhibits C4 and C5 indicate that the National Library of Medicine holds volume 96 in the section titled: Availability: v.1 (1946)-v.122; no.20 (2013) indicates that all volumes from v.1 through v.122, no. 20, are held by the National Library of Medicine including volume 96.

57. Allowing for a week at the most between the date stamp, November 9, 2000, and the issue's availability on the shelf, it would have been available no later than mid-November 2000.

58. Exhibit C6 is further evidence that the Hideshima paper was publicly available no later than April 2001. The Hideshima paper is cited as number 27 in References on page 3076 of the article by Tera Hideshima, et al., entitled "The Proteasome Inhibitor PS341 Inhibits Growth, Induces Apoptosis, and Overcomes Drug Resistance in Human Multiple Myeloma Cells," published in Cancer Research, Volume 61, Issue 7: 3071-3076, in April 2001.

3. *Conclusion*

59. Based on the evidence presented here—publication in a widely held journal, online indexing and publication, and library processing—it is my opinion that the Hideshima paper (attached as Exhibit C1 and Exhibit C2 (Exhibit 1016)) is an authentic document. It is also my opinion that the Hideshima paper was publicly available to researchers no later than mid-November 2000. Thus, in my opinion, the Hideshima paper was sufficiently accessible to the public interested in the art, such

that an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of the Hideshima article in the journal Blood no later than mid-November 2000.

D. Corral, L.G., et al., "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," Journal of Immunology, Volume 163, Number 1, (July 1, 1999): 380-386. (Corral I)

1. *Authentication*

60. "Corral I" refers to a research paper by L. G. Corral, et al., "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," published in the Journal of Immunology, Volume 163, Number 1 (July 1, 1999), pages 380-386. I requested a copy of the Corral I paper from the Wisconsin Tech Services (WTS) which provided scans from a print copy held in the Health Sciences Library, University of Wisconsin.

61. Exhibit D1 is a true and accurate copy of the cover/title page, table of contents and the Corral I paper from the print issue of the Journal of Immunology, Volume 163, Number 1 (July 1, 1999), pages 380-386. On the cover of the issue/title page is the ownership and date stamp of the Health Sciences Library, University of Wisconsin, that shows a check-in date of June 25, 1999.

62. Exhibit D1 is a true and accurate copy of the Corral I paper from the print copy owned by the Health Sciences Library of the University of Wisconsin. The copy of the Corral I paper in Exhibit D1 is not missing any intermediate pages

of the article's text, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document. Exhibit D1 was found within the custody of a library – a place where, if authentic, it would likely be housed and available.

63. The Corral I paper is also readily available online. Exhibit D2 is a true and accurate copy of the Corral I paper that I downloaded through the Journal of Immunology website: http://www.jimmunol.org/content/jimmunol/163/1/380.full .pdf on August 18, 2018 – a place where, if authentic, the Corral I paper would likely be found and made available. Based on my review, the text and figures of Exhibit D2 are the same as Exhibit D1. Exhibit D2 was filed as Exhibit 1009 in this proceeding.

64. I conclude, based on finding the Corral I paper in print, in both a library and online through a reputable, disciplinary database, that the Corral I paper is an authentic document and that Exhibit D1 and Exhibit D2 (Exhibit 1009) are authentic copies of the Corral I paper.

2. *Public Accessibility*

65. Exhibit D3 is a true and accurate copy of the record in OCLC WorldCat for the Journal of Immunology. The OCLC WorldCat record indicates that the Journal of Immunology shows 281 libraries world-wide holding the Journal of Immunology. Exhibit D3 indicates that the Journal of Immunology was cataloged

and indexed in a meaningful way—including by title and by subject, including Immunology – Periodicals; Immunity – Periodicals; and Hypersensitivity.

66. Exhibit D4 is the OPAC (online catalog) and MARC records for the Journal of Immunology from the University of Wisconsin Library. The University of Wisconsin OPAC record indicates that the library has held this title in print from its start in 1916, through its various change in title.

67. Allowing for a week at the most between the date stamp, June 25, 1999, and the issue's availability on the shelf, it would have been available no later than the first week of July 1999.

68. Exhibit D5 is further evidence that the Corral I paper was publicly available no later than January 31, 2001. The Corral I paper is cited as number 25 in References on page 22387 of the article by Jayne A. Keifer, et al., titled "Inhibition of NF-kB Activity by Thalidomide through Suppression of IkB Kinase Activity," published in the Journal of Biological Chemistry, volume 276, number 25, issue of June 22, 2001 (article received for publication, January 31, 2001).

3. *Conclusion*

69. Based on the evidence presented here—publication in a widely held journal, online indexing and publication, and library processing—it is my opinion that the Corral I paper (attached as Exhibit D1 and Exhibit D2 (Exhibit 1009)) is an authentic document. It is also my opinion that the Corral I paper was publicly

available to researchers no later than the first week of July 1999. Thus, in my opinion, the Corral I paper was sufficiently accessible to the public interested in the art, such that an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of the Corral I paper in the Journal of Immunology no later than the first week of July 1999.

E. Corral, L., and Kaplan, G., "Immunomodulation by thalidomide and thalidomide analogues," Annals of the Rheumatic Diseases, Volume 58, Supplement, Number 1 (November 1999): 107-113. (Corral II)

1. *Authentication*

70. "Corral II" refers to a research paper by L. G. Corral and G. Kaplan, "PMCID: PMC1766578 Immunomodulation by Thalidomide and Thalidomide Analogues," published in the Annals of the Rheumatic Diseases, volume 58, Supplement Number 1 (November 1999), pages 107-113. I requested a copy of the Corral II paper from the Wisconsin Tech Services (WTS) which provided scans from a print copy held in the National Library of Medicine located in Bethesda, Maryland.

71. Exhibit E1 is a true and accurate copy of the cover/title page, table of contents and the Corral II article from the print issue of the Annals of the Rheumatic Diseases, volume 58, supplement, number 1 (November 1999), pages 107-113. On the cover of the issue is the ownership label of the National Library of Medicine, which shows a receipt date of December 1999 (the day of the month was most likely cut off in binding or missed in scanning).

72. Exhibit E1 is a true and accurate copy of the Corral II paper from the print copy owned by the National Library of Medicine. The copy of the Corral II paper in Exhibit E1 is not missing any intermediate pages of the article's text, the text on each page appears to flow seamlessly from one page to the next, and there are no visible alterations to the document. Exhibit E1 was found within the custody of a library – a place where, if authentic, it would likely be housed and available.

73. The Corral II paper is also readily available online. Exhibit E2 is a true and accurate copy of the Corral II paper that I downloaded through the BMJ website: https://ard.bmj.com/ on August 19, 2018 – a place where, if authentic, the Corral II paper would likely be found and made available. Based on my review, the text and figures of Exhibit E2 are the same as Exhibit E1. Exhibit E2 was filed as Exhibit 1010 in this proceeding.

74. I conclude, based on finding the Corral II paper in print, in both a library and online through a reputable, disciplinary database, that the Corral II paper is an authentic document and that Exhibit E1 and Exhibit E2 (Exhibit 1010) are authentic copies of the Corral II paper.

2. *Public Accessibility*

75. Exhibit E3 is a true and accurate copy of the record in OCLC WorldCat for the Annals of the Rheumatic Diseases. The OCLC WorldCat record indicates that the Annals of the Rheumatic Diseases shows 1049 libraries world-wide holding

the Annals of the Rheumatic Diseases. Exhibit E3 indicates that the Annals of the Rheumatic Diseases was cataloged and indexed in a meaningful way—including by title and by subject, including: Rheumatism – Periodicals; and Rheumatism.

76. Exhibit E4 is the OPAC (online catalog) and MARC records for the Annals of the Rheumatic Diseases from the National Library of Medicine (NLM). The NLM OPAC and MARC records indicate that NLM has held this title in print from its start with volume 1, number 1 in May, 1939.

77. Allowing for a week at the most between the date stamp, December 1999, and the issue's availability on the shelf, it would have been available no later than the first week of January 2000.

78. Exhibit E5 is further evidence that the Corral II paper was publicly available elsewhere by November 2000 at the latest. The Corral II paper is cited as number 93 in References on page i71 of the article by Alisa Erika Koch, entitled "The Role of Angiogenesis in Rheumatoid Arthritis: Recent Developments" published in the Annals of the Rheumatoid Diseases, volume 59, Supplement 1:i65-i71, on November 1, 2000.

3. *Conclusion*

79. Based on the evidence presented here—publication in a widely held journal, online indexing and publication, and library processing—it is my opinion that the Corral II paper (attached as Exhibit E1 and Exhibit E2 (Exhibit 1010)) is an

authentic document. It is also my opinion that the Corral II paper was publicly available to researchers no later than the first week of January 2000. Thus, in my opinion, the Corral II paper was sufficiently accessible to the public interested in the art, such that an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of the Corral II paper in the Annals of the Rheumatic Diseases no later than the first week of January 2000.

V. CONCLUSION

80. In view of the foregoing, it is my opinion that the publications described above were publicly available no later than the corresponding date listed in the table below:

Exhibits	**Publication**	**Publicly Available No Later Than**
Exhibit A1 Exhibit A2 Exhibit 1015	Palumbo, A., et al., "Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma," Haemtologica. Volume 86, Number 4 (April 2001): 399-403. (Palumbo)	End of May 2001
Exhibit B1 Exhibit B2 Exhibit 1008	Muller, G.W., et al., "Amino-substituted thalidomide analogs: potent inhibitors of TNF-alpha production," Bioorganic and Medicinal Chemistry Letters. Volume 9, Number 11 (June 7, 1999): 1625-30. (Muller)	End of June 1999
Exhibit C1 Exhibit C2 Exhibit 1016	Hideshima, T., et al., "Thalidomide and its analogs overcome drug resistance of human multiple myleloma cells to conventional therapy," Blood, Volume 96, Number 9 (November 1, 2000): 2943-50. (Hideshima)	Mid-November 2000

Exhibit D1 Exhibit D2 Exhibit 1009	Corral, L.G., et al., "Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha," Journal of Immunology, Volume 163, Number 1 (July 1, 1999): 380-386. (Corral I)	First week of July 1999
Exhibit E1 Exhibit E2 Exhibit 1010	Corral, L., and Kaplan, G., "Immunomodulation by thalidomide and thalidomide analogues," Annals of the Rheumatic Diseases, Volume 58, Supplement, Number 1 (November 1999): 107-113. (Corral II)	First week of January 2000

81. I reserve the right to supplement my opinions in the future to respond to any arguments that Patent Owner or its expert(s) may raise and to take-into account new information as it becomes available to me.

82. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed this 10th day of September, 2018, in Williamsburg, Virginia

James L. Mullins, PhD

Appendix A

James L. Mullins

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Experience:

2018-	**Dean of Libraries Emeritus and Esther Ellis Norton Professor Emeritus**
2011 - 2017	**Dean of Libraries & Esther Ellis Norton Professor**
2004 - 2011	**Dean of Libraries & Professor** **Purdue University, West Lafayette, IN.**
2000-2004	**Assistant/Associate Director for Administration, MIT Libraries, Massachusetts Institute of Technology, Cambridge, MA.**
1996-2000	**University Librarian & Director, Falvey Memorial Library. Villanova University, Villanova, PA.**
1978-1996	**Director of Library Services, Indiana University South Bend.**
1974-1978	**Associate Librarian, Indiana University Bloomington, School of Law.**
1973-1974	**Instructor/Catalog Librarian. Georgia Southern College (now University)**.

Teaching Experience:

1977-1996	**Associate Professor (part-time), School of Library and Information Science, Indiana University. Subjects taught: cataloging, management, academic library administration.**

Education:

The University of Iowa. Honors Bachelor of Arts in History, Religion and Political Science.
The University of Iowa. Master of Arts in Library Science.
Indiana University. Doctor of Philosophy. Concentration: Academic Library Administration. Emphasis: Legal Librarianship.

Awards and Recognition:

2017 Wilmeth Active Learning Center/Library of Engineering and Science, Grand Reading Room, announced its re-naming to the James L. Mullins Reading Room, by President Mitch Daniels, Purdue University to honor Dean Mullins, September 2017. Portrait unveiled December, 2017.

2017 Distinguished Alumnus Award by the School of Informatics and Computing, Indiana University, Bloomington. Given June 25, 2017.

2016 Hugh C. Atkinson Memorial Award, that recognizes national leadership in the library profession, jointly sponsored by the four divisions of the American Library Association (ALA), June 27, 2016.

2015 ACRL Excellence in University Libraries Award, April 23, 2015.

Named Esther Ellis Norton Professor of Library Science by Purdue Trustees, December 11, 2011.

International Review Panel to evaluate the University of Pretoria Library, February 20 – 24, 2011. Pretoria, South Africa.

Publications: (selected)

A Purdue Icon: creation, life, and legacy, edited by James L. Mullins, Founder's Series, Purdue University Press, 138pp., August, 2017.

"The policy and institutional framework." In *Research Data Management, Practical Strategies for Information Professionals*, edited by Ray, J M. Purdue University Press, pp.25-44, 2014.

"DataCite: linking research to data sets and content." In Benson, P and Silver, S. *What Editors Want: An Author's Guide to Scientific Journal Publishing*. University of Chicago Press, pp. 21-23, December 2012.

"Library Publishing Services: Strategies for Success," with R. Crow, O. Ivins, A. Mower, C. Murray-Rust, J. Ogburn, D Nesdill, M. Newton, J. Speer, C. Watkinson. *Scholarly Publishing and Academic Resources Coalition (SPARC)*, version 2.0, March 2012.

"The Changing Definition and Role of Collections and Services in the University Research Library." *Indiana Libraries*, Vol 31, Number 1 (2012), pp.18-24.

"Are MLS Graduates Being Prepared for the Changing and Emerging Roles that Librarians must now assume within Research Libraries?" *Journal of Library Administration.* Volume 52, Issue 1, 2012, p. 124-132

Baykoucheva, Svetla. What Do Libraries Have to Do with e-Science?: An Interview with James L. Mullins, Dean of Purdue University Libraries. Chem. Inf. Bull. [Online] 2011, 63 (1), 45-49. http://www.acscinf.org/publications/bulletin/63-1/mullins.php (accessed Mar 16, 2011).

"The Challenges of e-Science Data-set Management and Scholarly Communication for Domain Sciences and Technology: a Role for Academic Libraries and Librarians," chapter in, *The Digital Deluge: Can Libraries Cope with e-Science?"* Deanna B. Marcum and Gerald George, editors, Libraries Unlimited/Teacher Ideas Press, 2009. (a monograph publication of the combined proceedings of the KIT/CLIR proceedings).

"Bringing Librarianship to e-Science," *College and Research Libraries.* vol. 70, no. 3, May 2009, editorial.

"The Librarian's Role in e-Science" *Joho Kanri (Journal on Information Processing and Management)*, Japan Science and Technology Agency (formerly Japan Information Center of Science and Technology), Tokyo, Japan. Translated into Japanese by Taeko Kato. March, 2008.

The Challenge of e-Science Data-set Management to Domain Sciences and Engineering: a Role for Academic Libraries and Librarians," KIT (Kanazawa

Institute of Technology)/CLIR (Council of Library and Information Resources) International Roundtable for Library and Information Science, July 5-6, 2007. Developments in e-science status quo and the challenge, The Japan Foundation, 2007.

"An Administrative Perspective," Chapter 14, *Proven Strategies for Building an Information Literacy Program*, Susan Curzon and Lynn Lampert, editors, Neal-Schuman Publishers, Inc., New York, 2007. pp. 229-237. .

Library Management and Marketing in a Multicultural World, proceedings of the IFLA Management and Marketing (M&M) Section, Shanghai, China, August 16-17, 2006, edited.
K.G. Saur, Munchen, Germany, June 2007. 390 pp.

Top Ten Assumptions for the Future of Academic Libraries and Librarians: a report from the ACRL Research Committee, with Frank R. Allen and Jon R. Hufford. *College & Research Libraries*, April 2007, vol.68, no.4. pp.240-241, 246.

To Stand the Test of Time: Long-term Stewardship of Digital Data Sets in Science and Engineering. A report to the National Science Foundation from the ARL Workshop on New Collaborative Relationships: the Role of Academic Libraries in the Digital Data Universe. September 26-27, 2006, Arlington, VA. p.141. http://www.arl.org/bm~doc/digdatarpt.pdf

"Enabling Interaction and Quality in a Distributed Data DRIS," *Enabling Interaction and Quality: Beyond the Hanseatic League*. 8th International Conference on Current Research Information Systems, with D. Scott Brandt and Michael Witt. Promoted by euro CRIS. Leuven University Press, 2006. pp.55-62. Editors: Anne Garns Steine Asserson and Eduard J. Simons.

"Standards for College Libraries, the final version approved January 2000," prepared by the ACRL College Libraries Standards Committee (member), *C&RL News*, March 2000, p.175-182.

"Standards for College Libraries: a draft," prepared by the ACRL College Libraries Section, Standards Committee (member), *C&RL News*, May, 1999, p. 375-381.

"Statistical Measures of Usage of Web-based Resources," *The Serials Librarian*, vol. 36, no. 1-2 (1999) p. 207-10.

(On a lighter note) "Philly's dining Renaissance," *American Libraries*, vol. 30, no. 1 (Jan. 99) p. 86-90. With Susan Markley. A guide to the restaurants for the American Library Association Meeting in Philadelphia in 1999.

"An Opportunity: Cooperation between the Library and Computer Services," in *Building Partnerships: Computing and Library Professionals.* Edited by Anne G. Lipow and Sheila D. Creth. Berkeley and San Carlos, CA, Library Solutions Press, 1995. p. 69-70.

"Faculty Status of Librarians: A Comparative Study of Two Universities in the United Kingdom and How They Compare to the Association of College and Research Libraries Standards, " in *Academic Librarianship, Past, Present, and Future: a Festschrift in Honor of David Kaser.* Englewood, Colorado; Libraries Unlimited, 1989. p. 67-78. Review in: *College & Research Libraries*, vol. 51, no. 6. November 1990, p. 573-574.

Presentations: (Representative)

"How Long the Odyssey? Transitioning the Library and Librarians to Meet the Needs and Expectations of the 21st Century University," David Kaser Lecture, School of Informatics & Computing, Indiana University, Bloomington, IN, November 16, 2015.

Presentation at University of Cape Town, Cape Town, South Africa, August 20, 2015.

"The Challenge of Discovering Science and Technology Information," Moderator, International Federation of Library Associations (IFLA) Science and Technological Libraries Section Program, Cape Town, South Africa, August 18, 2015.

"An Odyssey in Data Management: Purdue University," International Federation of Library Associations (IFLA) Research Data Management: Finding Our Role – A program of the Research Data Alliance, Cape Town, South Africa, August 17, 2015.

Presentation at University of Pretoria, Pretoria, South Africa, August 11, 2015.

Co-Convener with Sarah Thomas, Harvard University, at the Harvard Purdue Symposium on Data Management, Harvard University, Cambridge, MA, June 15-18, 2015.

"Strategic Communication," panel discussion on the Director's role and perspective on library communications at Committee on Institutional Cooperation (CIC) Center for Library Initiatives (CLI) Annual Conference, University of Illinois Urbana-Champaign, May 20, 2015.

"Issues in Data Management," panel discussion moderated by Catherine Woteki, United States Undersecretary for Research, Education & Economics at 20th Agriculture Network Information Collaborative (AgNIC) Annual Meeting in the National Agricultural Library, Beltsville, MD, May 6, 2015.

"Active learning/IMPACT & the Active Learning Center at Purdue University," Florida Institute of Technology, Melbourne, FL, February 11, 2015.

"Science+art=creativity: libraries and the new collaborative thinking," panel moderator, International Federation of Library Associations (IFLA) 80th General Conference and Assembly, Lyon, France, August 19, 2014.

"Purdue University The Active Learning Center—A new concept for a library," Association of University Architects 59th Annual National Conference, University of Notre Dame, South Bend, IN, June 23, 2014.

"Big Data & Implications for Academic Libraries," keynote speaker, Greater Western Library Alliance (GWLA) Cyber-infrastructure Conference, Kansas City, MO, May 28, 2014.

"Research Infrastructure," panel moderator, Association of Research Libraries (ARL) 164th Membership Meeting, Ohio State University, Columbus, OH, May 7, 2014.

"An Eight Year Odyssey in Data Management: Purdue University," International Association of Scientific and Technological University Libraries (IATUL) 2013 Workshop Research Data Management: Finding Our Role, University of Oxford, UK, December 2013.

"Purdue University Libraries & Press: from collaboration to integration," Ithaka Sustainable Scholarship, The Evolving Digital Landscape: New Roles and

Responsibilities in Higher Education, libraries as publishers, New York, New York, October 2013.

"Tsinghua and Purdue: Research Libraries for the 21st Century," Tsinghua University, Tsinghua, China, August 2013.

"Purdue Publishing Experience in the Libraries Publishing Coalition," Association of American University Presses Annual Meeting, Press-Library Coalition Panel, Boston, Massachusetts,
June 21, 2013.

"Indiana University Librarians Day: Purdue University Libraries Ready for the 21st Century," Indiana University Purdue University Indianapolis (IUPUI), June 7, 2013.

"Purdue University Libraries and Open Access; CNI Project Update," Coalition for Networked Information, San Antonio, TX, April 5, 2013.

Memorial Resolution, honoring Joseph Brannon, to the Board of the Association of College & Research Libraries, Seattle, WA, January 2013.

"An overview of sustaining e-Science collaboration in an Academic Research Library—the Purdue experience," Duraspace e-Science Institute webcast, October 17, 2012.

"The Role of Libraries in Data Curation, Access, and Preservation: an International Perspective," Panel Moderator, 78th General Conference and Assembly, International Federation of Library Associations, Helsinki, Finland, August 15, 2012.

"21st Century Libraries," moderator of First Plenary Session, International Association of Technological University Libraries 33rd Annual Conference, Singapore, June 4, 2012.

"Planning for New Buildings on Campus," panel presenter, University of Calgary Building Symposium on Designing Libraries for the 21st Century, Calgary, Alberta, Canada, May 17, 2012.

"Data Management and e-Science, the Purdue Response." Wiley-Blackwell Executive Seminar-2012, Washington, DC, March 23, 2012.

"An overview of Sustaining e-Science Collaboration in Academic Research Libraries and the Purdue Experience." Leadership & Career Development Program Institute, Association of Research Libraries (ARL). Houston, TX, March 21, 2012.

"An overview of Data Activities at Purdue University in response to Data Management Requirements." Coalition for Academic Scientific Computation (CASC). Arlington, VA, September 8, 2011.

"Getting on Track with Tenure," Association of College and Research Libraries (ACRL) Research Program Committee. Washington, DC, June 26, 2011.

"Integration of the Press and Libraries Collaboration to Promote Scholarly Communication," Association of Library Collections & Technical Services (ALCTS) Scholarly Communication Interest Group – American Library Association, New Orleans, Louisiana, June 25 2011.

"Cooperation for improving access to scholarly communication," with N. Lossau (Germany), C. Mazurek (Poland), J. Stokker (Australia), panel moderator and presenter, Second Plenary Session, International Association of Scientific and Technological University Libraries (IATUL) 32nd Conference 2011, Warsaw, Poland. May 29-June 2, 2011.

"Riding the Wave of Data," STM Annual Spring Conference 2011. Trailblazing & transforming scholarly publishing **2011**. Washington, D.C., April 28, 2011.

"Confronting old assumptions to assume new roles: physical and operational integration of the Press and Libraries at Purdue University," keynote speaker, 2011 BioOne Publishers & Partners Meeting. Washington, D. C., April 22, 2011.

"Are MLS Graduates Being Prepared for the Changing and Emerging Roles that Librarians must now assume within Research Libraries?" University of Oklahoma Libraries Seminar, March 4, 2011, Oklahoma City, Oklahoma.

"The Future Role of University Librarians," the University of Cape Town, South Africa, February 25, 2011.

"New Roles for Librarians: the Application of Library Science to Scientific/Technical Research – Purdue University – a case study. International Council for Science and Technology (ICSTI); Ottawa, Canada. June 9, 2009.

"Reinventing Science Librarianship: Models for the Future," Association of Research Libraries / Coalition for Networked Information. October 16-17th, 2008, Arlington, VA. Moderator and convener of Data Curation: Issues and Challenges.

"Practical Implementation and Opportunities Created at Purdue University," African Digital Curation Conference, Pretoria, South Africa, (live video transmission), February 12, 2008.

Keynote speaker. "*Scholarly Communication & Academe: The Winter of Our Discontent,"* XXVII Charleston Conference on Issues in Book and Serial Acquisition, Charleston, South Carolina. November 8, 2007.

Keynote speaker. "*Enabling Access to Scientific & Technical Data-sets in e-Science: a role for Library and Archival Sciences,"* Greater Western Library Alliance (GWLA), Tucson, Arizona. September 17, 2007. A meeting of library directors and vice presidents for research of member institutions.

"*The Challenge of e-Science Data-set Management to Domain Sciences and Engineering: a Role for Academic Libraries and Librarians,"* KIT (Kanazawa Institute of Technology)/CLIR (Council of Library and Information Resources) International Roundtable for Library and Information Science, July 5-6, 2007. Invited to participate by the Deputy Librarian of Congress.

International Association of Technological University Libraries (IATUL), Stockholm, Sweden. June 8, 2007**.** Invited paper**,** *Enabling International Access to Scientific Data-sets: creation of the Distributed Data Curation Center (D2C2).*

"A New Collaboration for Librarians: The Principles of Library and Archival Sciences Applied to the Curation of Datasets," Symposium of the Libraries and the College of Engineering, University of Louisville, April 6, 2007.

"Purdue University Libraries: Through Pre-eminent Innovation and Creativity, Meeting the Challenges of the Information Age," Board of Trustees, Purdue University, February 15, 2007.

ARL Workshop on New Collaborative Relationships: The Role of Academic Libraries in the Digital Data Universe, September 26-27, 2006, Arlington, VA. Invited participant.

NARA and SDSC: A partnership. A panel before the National Science Foundation, June 27, 2006. Arlington, VA. Invited participant.

"Kaleidoscope of Scientific Literacy: fusing new connections," with Diane Rein, American Library Association, Association of College and Research Libraries, Science & Technology Section, Annual Conference, New Orleans, June 26th, 2006.

"Leadership for Learning: Building a Culture of Teaching in Academic Libraries – an administrative perspective," American Library Association, Association of College and Research Libraries, Instruction Section, Annual Conference, New Orleans, June 25th, 2006.

"Building an interdisciplinary research program in an academic library: how the Libraries'associate dean for research makes a difference at Purdue University," International Association of Technological University Libraries (IATUL), Porto, Portugal, May 23rd, 2006.

"Enabling Interaction and Quality in a Distributed Data DRIS," *Enabling Interaction and Quality: Beyond the Hanseatic League*. 8th International Conference on Current Research Information Systems, with D. Scott Brandt and Michael Witt. Promoted by euro CRIS, Bergen, Norway, May 12th, 2006, Brandt and Witt presented in person

"Interdisciplinary Research," with D. Scott Brandt, Coalition for Networked Information (CNI) Spring Meeting: Project Briefing, Washington, D.C., April 3rd, 2006.

"An Interview with Purdue's James Mullins," a podcast submitted by Matt Pasiewicz, on *Educause Connect*, http://connect.educause.edu/James_L_Mullins_Interview_CNI_2005

"Managing Long-Lived Digital Data-sets and their Curation: Interdisciplinary Policy Issues," Managing Digital Assets Forum, Association of Research Libraries (ARL), Washington, D.C., October 28th, 2005.

"The Odyssey of a Librarian." Indiana Library Federation (ILF), District 2 Meeting, South Bend, Indiana. October 4th, 2005.

"Is Anyone There?" LAMA, Statistics Section, ALA, Atlanta, June 19, 2002. Research presentation on librarian recruitment at the IvyPlus institutions during the last three years.

"New College Library Standards," Standards Committee Presentation, ALA, Chicago, July 7, 2000.

SUNY Library Directors, Lake George, New York. "*The College Library Standards: a Tool for Assessment."* April 5, 2000.

Tri-State College Library Association, *Finding You Have Talents You Never Knew You Had,* Penn State Great Valley, March 25, 2000.

Using Web Statistics, American Library Association, New Orleans, June 24, 1999.

Keynote speaker at the JSTOR Workshop, January 29, 30, 1999. University of Pennsylvania, Philadelphia, PA.

"The New Standards for Electronic Resources Statistics," Society of Scholarly Publishers, Washington, D.C., September 17, 1998.

"Evaluating Online Resources: Now that you've got them what do you do?," joint presenter with Chuck Hamaker, LSU, at the NASIG Conference, Boulder, Colorado. June 1998.

"What Employers Are Looking for in New Librarians?" Pennsylvania Library Association, Philadelphia. September 26, 1997.

"The Theory of Matrix Management" panel presentation of the Comparative Library Organization Committee of the Library Organization and Management Section of the Library Administration and Management Association, a division of the American Library Association, Annual Meeting, Chicago, June 24, 1990.

Professional Involvement: (summary of recent emphasis)

The focus for my professional involvement and research has moved recently toward managing massive data-sets. This has resulted in working with faculty in the sciences and technology to determine how librarians can collaborate in managing, curating, and preserving data-sets for future access and documentation. This has included various speaking opportunities as well as participation in

planning with the National Science Foundation (NSF) on ways in which librarians can be integrated more completely into the funded research process. Participation in the Kanazawa Institute of Technology/Council of Library Resources Roundtable was particularly rewarding and provided new opportunities to share with international colleagues the issues surrounding data-set management. I was the champion for the creation of the Distributed Data Curation Center (D2C2) at Purdue University (http://d2c2.lib.purdue.edu/)

Throughout my career, beginning with my dissertation, I have been actively involved with assessing and evaluating libraries. In the fall of 1999, I contacted twenty-two academic library directors to determine whether the need was also felt by others. The response was overwhelmingly affirmative. This resulted in a meeting at ALA Midwinter, January, 2000. A formal meeting followed at Villanova University in April, 2000. As convenor, I helped to form the University Libraries Group (ULG), modeled after the Oberlin Group for college libraries. The ULG is made up of university libraries that support diverse wide ranging programs through doctoral level, and have a level of support that places them in the top tier of academic institutions. A few of the member libraries, along with Villanova, are William and Mary, Wake Forest, Lehigh, Carnegie-Mellon, Tufts, Marquette, Miami of Ohio, and Southern Methodist.

In 1994, I was appointed to the Standards Committee, College Section, Association of College and Research Libraries. During the next six years, the Committee concentrated on changing the focus of the standards from quantitative analysis of input and output factors to emphasis on assessment of the outcome. Culmination of the work was a re-issue of the *Standards for College Libraries* in 2000. The knowledge gained through my work experience enabled me to formulate the changes needed in the standards. This work allowed for close collaboration with accrediting agencies, both professional and regional.

During this same time another focus emerged, the impact of digital resources. Through my work on the JSTOR Statistics Task Force, standards were developed on the collection of use of electronic databases. This Standard was later adopted in 1998 by the International Consortium of Library Consortia (ICOLC).

In 2002, the American Library Association appointed me to serve as the liaison to the Marketing and Management Section of the International Federation of Library Associations (IFLA).

Professional Service: (representative list)

Nominations Committee, Association of Research Libraries (ARL), 2016.

Steering Committee, Scholarly Publishing and Academic Resources Coalition (SPARC), 2016 – 2017.

"Excellence in Library Services," Chair, Review Team, University of Hong Kong, Hong Kong, August 24-27, 2015.

Chair, Management Advisory Board, 2015-2017; Member, Scientific Advisory Board, arXiv, Cornell University, 1/1/2013 – present.

Advisory Board for the Wayne State University School of Library and Information Science, July 2012 – present.

Advisory Board for Microsoft Academic Search, 2012 – 2015. Redmond, WA.

Transforming Research Libraries, a Strategic Direction Steering Committee of the Association of Research Libraries (ARL), 2012-2015.

Science and Technology section, representing ARL, International Federation of Library Associations (IFLA), Chair, 2013 – 2017; Member, 2011 to present.

Member of University of Pretoria, South Africa, Library Review Committee. August, 2013.

Co-chair, Local Arrangements Planning Committee for 2013 Conference, Association of College and Research Libraries (ACRL), a division of the American Library Association (ALA).

Association of Research Libraries Leadership & Career Development Program Mentor, 2011-2017.

e-Science Task Force, Association of Research Libraries. July 2006 – present. Chair, October 2011 – October 2012.

Board of Directors, International Association of Technological University Libraries (IATUL). January 2008 – December 2014.

Midwest Collaborative for Library Services (MCLS); Board Member, October 2010 – December 2012.

Chair, Library Directors, Committee on Institutional Cooperation (CIC), July 2010 – June 2012.

Board of Directors, Association of Research Libraries (ARL); October 2008 – October 2011.

Scholarly Communication Steering Committee, Association of Research Libraries (ARL)
2008-2011.

Editorial Board, *College and Research Libraries*, Association of College and Research Libraries, American Library Association. January 2008 – December 2014.

Chair, Organizing Committee for IATUL Conference 2010, June 21-24, 2010, Purdue University, West Lafayette, Indiana/Chicago, Illinois.

Conference Planning Committee for National Conference of the Association of College and Research Libraries, 2009, Seattle, Washington.

Research Committee, Association of College and Research Libraries, ACRL, division of ALA. 2002-2007, chair, 2005-2007.

Association of Research Libraries, Search and Screen Committee, Executive Director. March – January 2008.

Center for Research Libraries, Board of Directors. April 2006 – April 2012.

Academic Libraries of Indiana, Board of Directors, 2004 – 2017. Vice-president, 2005-2007. President, 2007- 2009.

ALA Representative to the International Federation of Library Associations (IFLA), Marketing and Management (M&M) Section, initial term 2003-2007, re-appointed for second term, 2007-2011.

ALA Nominating Committee - 2005. Appointed as LAMA representative.

Invited to represent Research Libraries at the ACRL/3M Wonewok Retreat to assess Marketing of Academic Libraries, October, 2002.

Hugh A. Atkinson Award Committee, LAMA Representative, ALA, 2001-2005.

Program Committee, Library Administrators and Management Association (LAMA), a division of ALA. 1996-2001.

ACRL, Standards and Accreditation Committee, a division of ALA. Liaison to RBMS Section of ACRL. 1997-2002.

Elected to the Executive Committee of LAMA, LOMS, a division of the American Library Association, 1998-2000. Nominated as Chair/Elect for 2003 – 2005.

Columbia University Press Advisory Committee. 1996 - 2000.

LITA/LAMA Conference Evaluation Committee, Pittsburgh, Pennsylvania, October, 1996.

"New Learning Communities," Coalition for Networked Information, Indianapolis. November 19-21, 1995. Facilitator for invitational, national conference committed to developing collaborative learning and teaching techniques, involving librarians.

Planning Committee-Evaluation. LITA/LAMA 1996 Conference, Pittsburgh. This first conference, to be held jointly between two divisions of ALA, will focus on new technologies within libraries.

Indiana Cooperative Library Services Authority (InCoLSA), elected to Executive Committee, April 1991, served as President in 1993-94. InCoLSA is a statewide network of academic, public, school and special libraries that supports library cooperation for cataloging, interlibrary loan, collection development and application of new technologies.

Governor's Conference on Libraries and Information Services. Served on Planning Committee, Academic Libraries Representative, appointed by the Governor to represent academic libraries in Indiana, Chair, Finance Committee, April, 1989-July 1991.

Indiana Library Endowment Foundation Board, 1984-92. Charter Member, 1984, President, 1988-1992. 2004-2005.

University Service: (Summary)

During my career I have served on search and screen committees for senior positions including chancellor, dean and directors; most recently I have been asked to serve on the search committee for the provost of Purdue University. At MIT service included the Library Council & appointment to the Administrative Council by President Vest, 2001-2003 & Member of the Faculty Committee on the Library System. At Purdue appointed by the President to the Search Committee for the Provost, October 2007 to May 2008; member of the Capital Projects Committee, and IT Operational Oversight Committee as senior academic dean, 2008-2014; Global Council, Global Policy Institute, 2012 – 2016.
Academic Program Excellence and Rankings (APER) project team, 2014.
Representative of the Academic Deans on the Re-engineering Business Operations, Purdue University, 2016 –
Academic Deans Council chaired by Provost – 2004 – 2017.
University Promotion and Tenure Committee – 2006 – 2017.

EXHIBIT A1

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5. Karlsson S, Humphries RK, Gluzman Y, Nienhuis AW. Transfer of genes into hemopoietic cells using recombinant DNA viruses [abstract]. Blood 1984; 64(Suppl 1):58a.

Books and other monographs (personal authors,[6,7] chapter in a book,[8] published proceeding paper,[9] abstract book,[10] monograph in a series,[11] agency publication[12]):

6. Ferrata A, Storti E. Le malattie del sangue. 2nd ed. Milano: Vallardi; 1958.
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Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma

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Background and Objectives. The immunomodulatory drug thalidomide can inhibit angiogenesis and induce apoptosis in experimental models. It can also induce marked and durable response in advanced myeloma patients. Thalidomide has been used at doses ranging from 200 to 800 mg with significant toxicity. No data are available on the impact of low-dose thalidomide plus dexamethasone as salvage therapy for relapsed patients.

Design and Methods. To address this issue, myeloma patients were treated with 100 mg/day thalidomide continuously and dexamethasone 40 mg, days 1-4, every month. Between June 1999 and August 2000, 77 patients (median age 65 years) who had relapsed or were refractory to chemotherapy were treated with thalidomide plus dexamethasone.

Results. After a minimum of 3 months of treatment, 14 patients (18%) showed a myeloma protein reduction of 75%-100%, 18 patients (23%) showed a response of 50-75%, 19 patients (25%) a response of 25-50% and 26 patients (34%) a response of <25% or disease progression. After a median follow-up of 8 months, median progression-free survival was 12 months. Thalidomide was well tolerated. Constipation (12%) and sedation (6%) were mild. Tingling or numbness were present in 17% of patients, discontinuation of treatment was required in 10% of patients.

Interpretation and Conclusions. The association of low-dose thalidomide plus dexamethasone is active against advanced myeloma. A significant proportion of patients benefit from this treatment as a salvage therapy postponing the delivery of chemotherapy.

Key words: myeloma, thalidomide, dexamethasone, salvage therapy

Angiogenesis is increased in multiple myeloma and has a prognostic value in the disease.[1,2] The antiangiogenic properties of thalidomide[3] provide the rationale for studying the effect of this drug in myeloma. Thalidomide may directly inhibit the growth and survival of myeloma cells;[4] its efficacy may also be linked to modulation of growth-related genes, such as c-myc.[5] The interleukin-6 (IL-6) receptor gene is also dramatically downregulated.[5]

For more than 30 years the initial therapy of multiple myeloma has consisted of melphalan and prednisone.[6-8] A therapeutic strategy to improve clinical outcome is high-dose chemotherapy followed by autologous stem cell transplantation.[9,10] Relapses, however, constantly occur and cure is rarely achieved.[11]

To improve treatment outcome and introduce the possibility of curative therapy, it is necessary to search for new drugs or new uses of old drugs. One such compound is thalidomide. This drug was found to be effective in refractory and recurrent myelomas producing an overall response rate of 32%.[12] The study design called for a gradual increase in the dose, but only 55% of the patients received the intended maximal daily dose of 800 mg. Most patients received 400 mg of thalidomide daily. Glucocorticoids are effective and extensively used in the management of patients with advanced myeloma.[13-15] *In vitro*, thalidomide enhanced the anti-myeloma activity of dexamethasone which, conversely, was inhibited by IL-6.[16]

Based on these pieces of evidence, we evaluated the toxicity and clinical efficacy of low-dose thalidomide combined with corticosteroids on the assumption that lower thalidomide doses are better tolerated and the association with corticosteroids may exert a synergistic effect. Refractory/relapsed myeloma patients were treated with this schedule. Low-dose thalidomide plus dexamethasone was shown to be extremely well tolerated and highly effective.

Design and Methods

Patients

Between June 1999 and August 2000, 77 consecutive patients with refractory or relapsed myeloma entered the protocol. The SWOG[17,18] and Durie and Salmon staging systems were used. At diagnosis, 37 patients were treated with high-dose chemotherapy (two or three courses of melphalan at 100 mg/m^2 as previously described),[19] and 40 were treated with conventional chemotherapy (32 received oral melphalan and prednisone, 8 dexamethasone-doxorubicin-vincristine). These regimens were also used as salvage therapy. Thalidomide plus dexamethasone was administered a median of 46 months after diagnosis. Four patients had primary resistance to induction treatment, 21 were in resistant relapse and 52 were in untested relapse. Twenty-six patients received thalidomide after one line of therapy, 21 after two and 30 after three. Among those receiving high-dose chemotherapy, 17 were in first untested relapse, 18 in second untested relapse and 2 were in resistant relapse. Of those treated with conventional chemotherapy, 4 had primary resistance, 19 were in resistant relapse and 17 in untested relapse. No patients were excluded on the basis of cardiac, renal, pulmonary or liver function. All patients were treated in two hematologic centers. Written informed consent was obtained from all patients.

Treatment

Thalidomide was supplied in 100 mg capsules by Grunenthal GmbH, 52222 Stolberg, Germany. Thalidomide was administered at the dose of 100 mg at bedtime and associated with dexamethasone administered orally at the dose of 40 mg on days 1, 2, 3, and 4 every month. Data were analyzed when the duration of thalidomide treatment ranged from 3 to 16 months (median 6.9). At the time of treatment, all patients had progressive disease with a >50% increase in myeloma protein or reappearance of Bence Jones proteinuria >0.5 g/24h. Pre-treatment evaluation included complete blood count, renal and liver function tests, serum and urine myeloma protein and serum β_2-microglobulin evaluation. Patients were evaluated for neurological abnormalities and electromyography was performed if clinical signs of neuropathy were detected. Patients were evaluated monthly and physical examination and blood test were routinely performed. The patient's characteristics are listed in Table 1.

Response criteria and statistics

Complete remission required disappearance of serum or urine myeloma protein analyzed by standard electrophoresis and marrow plasmacytosis <1% for at least 2 months. Clinical responses were defined according to the reduction of serum myeloma protein: 75%-100%, 50%-75%, 25%-50%, and <25%, respectively. In Bence Jones myeloma, disappearance of urine myeloma protein was recorded as a clinical response of 75%-100%. Clinical responses 50%-75%, and 25%-50% were defined when the reduction of urine myeloma protein was >90%, and >50%, respectively. All other results were recorded as failures. Progression was defined by increases in serum or urine myeloma protein >25%. The curve was plotted according to the method of Kaplan and Meier from the beginning of the treatment with thalidomide.[20]

Table 1. Patients' characteristics.

No. of patients	77
Median age (y)	65
Stage at diagnosis	
IIA	30
IIB	4
IIIA	40
IIIB	3
β2-microglobulin < 3 mg/mL	34
β2-microglobulin > 3 mg/mL	43
	% of patients
M-protein class	
IgG	60
IgA	27
IgM	1
Bence Jones protein	12
Bone marrow plasma cells > 30%	64
WHO performance status >3	13

Table 2. Response.

M-protein reduction	*No. of patients*	*% of total*	
75%-100%	14	18	41
50%-75%	18	23	
25%-50%	19	25	
No response*	26	34	

**Disease progression or stable disease or <25% M-protein reduction.*

Results

Response rate

The daily dose of thalidomide was reduced from 100 mg to 50 mg in 4% of patients and in 10% the administration of thalidomide was suspended after a median of 3 months (range 1-11). The monthly dose of dexamethasone was stopped in 1% of patients. All patients were considered in the evaluation: 41% showed a myeloma protein decline >50%: in 18% the decline was 75-100%, in 23% it was 50-75%, and in 25% it was 25-50% (Table 2). Three percent showed complete remission.

The median time required to obtain the maximum response to thalidomide plus dexamethasone was 4.2 months (range 0.6-10.2): 33% of maximum responses were apparent after 2 months, 15% after 3 months and 17% after 4 months; however, 35% became apparent

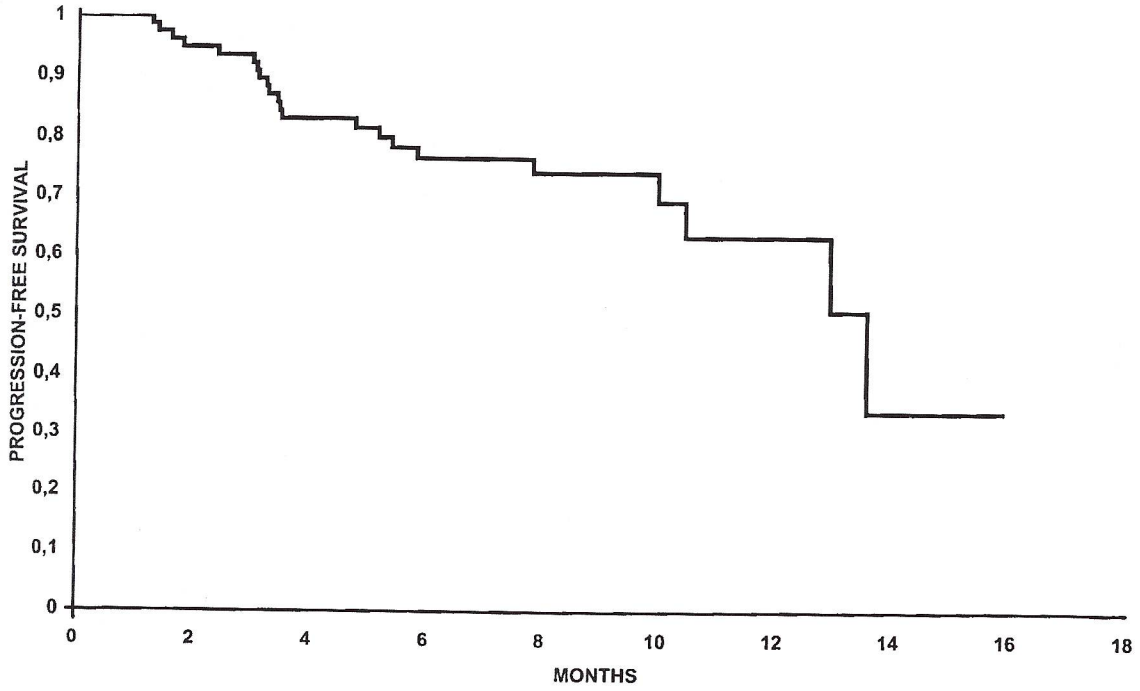

Figure 1. Progression-free survival of myeloma patients treated with thalidomide plus dexamethasone.

between 4 and 6 months. Improvement of performance status, skeletal pain, blood count, anemia and transfusion requirements were slower and related to the degree of response. After a response of 50-100%, the median levels of hemoglobin increased from 11 g/dL to 13 g/dL.

Clinical outcome

Among the 51 patients with a >25% decline in the myeloma protein, 10 showed disease recurrence. After a median follow-up of 8 months (range 3 to 16), the median time to progression was 12 months (Figure 1). The median overall survival was not reached and 91% of patients were alive.

Toxicity

Most adverse effects were recorded as grade I according to the World Health Organization toxicity classification. Thalidomide had to be discontinued because of toxicity in only 8 patients. Constipation was relatively frequent but well controlled with appropriate medication. Sedation was recorded in 6% of patients, changes in full-time or part-time working habits were required in 4% only. Weakness and fatigue were experienced in 8% of patients. These symptoms were drastically reduced when patients took thalidomide at dinnertime. Mood changes or depression were present in 4% of patients, but mainly in elderly subjects. Tingling and numbness were observed in an unexpected 14% of patients as grade I, in 3% as grade II. These symptoms developed after a median time of 3 months. Tingling required thalidomide discontinuation in 5% of patients, but 3% then experienced an improvement. Tremors and inco-ordination were present in 3% of patients and were generally mild. Dizziness was a late adverse effect (3%), and was mainly a clinical progression of foot numbness. One patient developed a severe skin rash on her face followed by vesicles and bullae: erysipelas was diagnosed and successfully treated with oral antibiotics. In another patient, a severe necrotic ulcer of the skull was observed. Two patients had evidence of hypothyroidism. Blood counts generally improved when disease response was achieved. Two patients showed an increase in creatinine levels. In one patient disease progression occurred with a slight increase in Bence Jones proteinuria accompanied by acute renal failure requiring dialysis. No concomitant nephrotoxic therapy was delivered in these subjects. Previously reported episodes of deep vein thrombosis were not observed (Table 3).[21]

Discussion

The association of low-dose thalidomide plus dexamethasone was highly effective in patients with relapsed or refractory myeloma: 41% showed a >50% decrease in myeloma protein. In most patients, the serological response was accompanied by a significant improvement of asthenia and bone pain, and a marked increase in hemoglobin levels. Oral melphalan and prednisone induced a tumor mass reduction >50% in only 20% of resistant/relapsing patients.[22] Our data clearly show that

Table 3. Toxicity.

	No. of patients	% of total
Tingling and numbness	13	17
Constipation	9	12
Weakness and fatigue	6	8
Sedation	5	6
Changes in work habit	3	4
Mood changes and depression	3	4
Tremor	2	3
Dizziness	2	3
Erysipela	2	3
Hypothyroidism	2	3
Renal toxicity	2	3
Toxicity that required discontinuation of treatment	8	10

low-dose thalidomide and dexamethasone have a true anti-tumor effect and that this is superior to that achieved by oral melphalan and prednisone.

Recent data suggest that thalidomide alone is active in 30-60% of patients with refractory/relapsed myeloma.[12,16,21,23,24] With doses ranging from 200 mg to 800 mg/day, side-effects were encountered in 10-50%.[12] In our study, adverse effects were recorded in 5-15%. In the escalating dose studies already performed, no relation between dose and response has been demonstrated.[12,21] In preliminary reports, a dose as low as 50 mg/day was claimed to be effective in myeloma patients.[25,26] In our series, median time to response was 4.2 months. This was longer than previously reported times, perhaps due to the lower dose of thalidomide.

The importance of glucocorticoids has been demonstrated by evaluating melphalan and prednisone administration in the primary management of myeloma. Survival time was found to correlate with the dose of prednisone and not with that of melphalan.[27] In refractory patients high doses of prednisone or dexamethasone may induce remission in a significant proportion of cases.[13,14]

Thalidomide and dexamethasone are a logical combination since they may differ in their action against myeloma. Thalidomide acts via adhesion molecule alteration, anti-angiogenesis and modulation of T-lymphocytes, whereas dexamethasone exerts its effect by inhibiting IL-6 production. *In vitro*, the addition of dexamethasone increased the inhibition of proliferation induced by thalidomide on myeloma cell lines by about 35%. Thalidomide induced apoptosis in cells resistant to dexamethasone, suggesting the potential utility of the combination of these two drugs.[16]

Here, we demonstrate that the combination of thalidomide at 100 mg/day plus dexamethasone at only 40 mg, 4 days each month, is an effective treatment against myeloma. At this dose dexamethasone alone cannot induce partial response in 40% of refractory patients. For these patients, 30% partial responses were recorded when dexamethasone was delivered at 40 mg but 12 days each month.[13] When thalidomide was administered alone at doses ranging from 200 mg to 800 mg partial responses were achieved in 25% of cases in one report[12] and 40% in another.[23]

In conclusion this study confirms previous findings showing that thalidomide is a new compound for the management of myeloma and is the first demonstration that low-dose thalidomide plus dexamethasone is an effective treatment for myeloma patients. The low-dose thalidomide schedule is very well tolerated and highly effective. Whether this efficacy is due to an additive or synergistic effect with dexamethasone is not clear.

Contributions and Acknowledgments

AnP conception, design, interpretation of data, drafting the article; LG, AB, PP SB, CR, ST analysis, interpretation of data, critical revision; EG, AP critical revision, important intellectual suggestions, final approval of the version to be submitted. MB conception, design, drafting the article, final approval of the version to be submitted.

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Potential implications for clinical practice

Low-dose thalidomide is well tolerated and highly effective on refractory myeloma. A significant proportion these patients benefit from this treatment as a salvage therapy postponing the delivery of chemotherapy.

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EXHIBIT A2

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Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma

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Background and Objectives. The immunomodulatory drug thalidomide can inhibit angiogenesis and induce apoptosis in experimental models. It can also induce marked and durable response in advanced myeloma patients. Thalidomide has been used at doses ranging from 200 to 800 mg with significant toxicity. No data are available on the impact of low-dose thalidomide plus dexamethasone as salvage therapy for relapsed patients.

Design and Methods. To address this issue, myeloma patients were treated with 100 mg/day thalidomide continuously and dexamethasone 40 mg, days 1-4, every month. Between June 1999 and August 2000, 77 patients (median age 65 years) who had relapsed or were refractory to chemotherapy were treated with thalidomide plus dexamethasone.

Results. After a minimum of 3 months of treatment, 14 patients (18%) showed a myeloma protein reduction of 75%-100%, 18 patients (23%) showed a response of 50-75%, 19 patients (25%) a response of 25-50% and 26 patients (34%) a response of <25% or disease progression. After a median follow-up of 8 months, median progression-free survival was 12 months. Thalidomide was well tolerated. Constipation (12%) and sedation (6%) were mild. Tingling or numbness were present in 17% of patients, discontinuation of treatment was required in 10% of patients.

Interpretation and Conclusions. The association of low-dose thalidomide plus dexamethasone is active against advanced myeloma. A significant proportion of patients benefit from this treatment as a salvage therapy postponing the delivery of chemotherapy.

Key words: myeloma, thalidomide, dexamethasone, salvage therapy

Angiogenesis is increased in multiple myeloma and has a prognostic value in the disease.[1,2] The antiangiogenic properties of thalidomide[3] provide the rationale for studying the effect of this drug in myeloma. Thalidomide may directly inhibit the growth and survival of myeloma cells;[4] its efficacy may also be linked to modulation of growth-related genes, such as c-myc.[5] The interleukin-6 (IL-6) receptor gene is also dramatically downregulated.[5]

For more than 30 years the initial therapy of multiple myeloma has consisted of melphalan and prednisone.[6-8] A therapeutic strategy to improve clinical outcome is high-dose chemotherapy followed by autologous stem cell transplantation.[9,10] Relapses, however, constantly occur and cure is rarely achieved.[11]

To improve treatment outcome and introduce the possibility of curative therapy, it is necessary to search for new drugs or new uses of old drugs. One such compound is thalidomide. This drug was found to be effective in refractory and recurrent myelomas producing an overall response rate of 32%.[12] The study design called for a gradual increase in the dose, but only 55% of the patients received the intended maximal daily dose of 800 mg. Most patients received 400 mg of thalidomide daily. Glucocorticoids are effective and extensively used in the management of patients with advanced myeloma.[13-15] *In vitro*, thalidomide enhanced the anti-myeloma activity of dexamethasone which, conversely, was inhibited by IL-6.[16]

Based on these pieces of evidence, we evaluated the toxicity and clinical efficacy of low-dose thalidomide combined with corticosteroids on the assumption that lower thalidomide doses are better tolerated and the association with corticosteroids may exert a synergistic effect. Refractory/relapsed myeloma patients were treated with this schedule. Low-dose thalidomide plus dexamethasone was shown to be extremely well tolerated and highly effective.

Design and Methods

Patients

Between June 1999 and August 2000, 77 consecutive patients with refractory or relapsed myeloma entered the protocol. The SWOG[17,18] and Durie and Salmon staging systems were used. At diagnosis, 37 patients were treated with high-dose chemotherapy (two or three courses of melphalan at 100 mg/m^2 as previously described),[19] and 40 were treated with conventional chemotherapy (32 received oral melphalan and prednisone, 8 dexamethasone-doxorubicin-vincristine). These regimens were also used as salvage therapy. Thalidomide plus dexamethasone was administered a median of 46 months after diagnosis. Four patients had primary resistance to induction treatment, 21 were in resistant relapse and 52 were in untested relapse. Twenty-six patients received thalidomide after one line of therapy, 21 after two and 30 after three. Among those receiving high-dose chemotherapy, 17 were in first untested relapse, 18 in second untested relapse and 2 were in resistant relapse. Of those treated with conventional chemotherapy, 4 had primary resistance, 19 were in resistant relapse and 17 in untested relapse. No patients were excluded on the basis of cardiac, renal, pulmonary or liver function. All patients were treated in two hematologic centers. Written informed consent was obtained from all patients.

Treatment

Thalidomide was supplied in 100 mg capsules by Grunenthal GmbH, 52222 Stolberg, Germany. Thalidomide was administered at the dose of 100 mg at bedtime and associated with dexamethasone administered orally at the dose of 40 mg on days 1, 2, 3, and 4 every month. Data were analyzed when the duration of thalidomide treatment ranged from 3 to 16 months (median 6.9). At the time of treatment, all patients had progressive disease with a >50% increase in myeloma protein or reappearance of Bence Jones proteinuria >0.5 g/24h. Pre-treatment evaluation included complete blood count, renal and liver function tests, serum and urine myeloma protein and serum β_2-microglobulin evaluation. Patients were evaluated for neurological abnormalities and electromyography was performed if clinical signs of neuropathy were detected. Patients were evaluated monthly and physical examination and blood test were routinely performed. The patient's characteristics are listed in Table 1.

Response criteria and statistics

Complete remission required disappearance of serum or urine myeloma protein analyzed by standard electrophoresis and marrow plasmacytosis <1% for at least 2 months. Clinical responses were defined according to the reduction of serum myeloma protein: 75%-100%, 50%-75%, 25%-50%, and <25%, respectively. In Bence Jones myeloma, disappearance of urine myeloma protein was recorded as a clinical response of 75%-100%. Clinical responses 50%-75%, and 25%-50% were defined when the reduction of urine myeloma protein was >90%, and >50%, respectively. All other results were recorded as failures. Progression was defined by increases in serum or urine myeloma protein >25%. The curve was plotted according to the method of Kaplan and Meier from the beginning of the treatment with thalidomide.[20]

Table 1. Patients' characteristics.

No. of patients	77
Median age (y)	65
Stage at diagnosis	
IIA	30
IIB	4
IIIA	40
IIIB	3
β2-microglobulin < 3 mg/mL	34
β2-microglobulin > 3 mg/mL	43
	% of patients
M-protein class	
IgG	60
IgA	27
IgM	1
Bence Jones protein	12
Bone marrow plasma cells > 30%	64
WHO performance status >3	13

Table 2. Response.

M-protein reduction	*No. of patients*	*% of total*	
75%-100%	14	18	} 41
50%-75%	18	23	
25%-50%	19	25	
No response*	26	34	

**Disease progression or stable disease or <25% M-protein reduction.*

Results

Response rate

The daily dose of thalidomide was reduced from 100 mg to 50 mg in 4% of patients and in 10% the administration of thalidomide was suspended after a median of 3 months (range 1-11). The monthly dose of dexamethasone was stopped in 1% of patients. All patients were considered in the evaluation: 41% showed a myeloma protein decline >50%: in 18% the decline was 75-100%, in 23% it was 50-75%, and in 25% it was 25-50% (Table 2). Three percent showed complete remission.

The median time required to obtain the maximum response to thalidomide plus dexamethasone was 4.2 months (range 0.6-10.2): 33% of maximum responses were apparent after 2 months, 15% after 3 months and 17% after 4 months; however, 35% became apparent

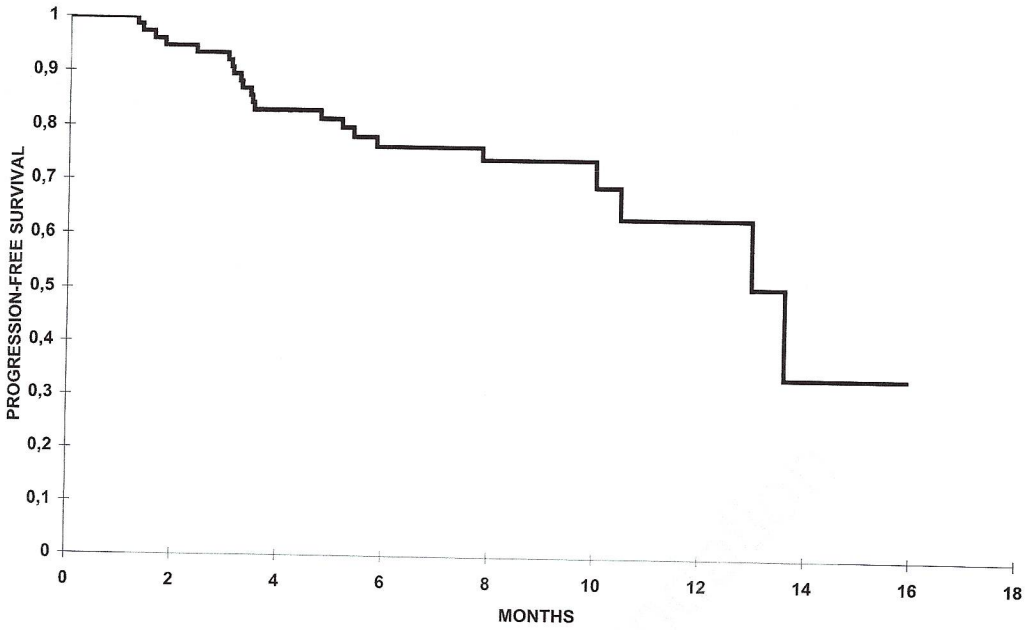

Figure 1. Progression-free survival of myeloma patients treated with thalidomide plus dexamethasone.

between 4 and 6 months. Improvement of performance status, skeletal pain, blood count, anemia and transfusion requirements were slower and related to the degree of response. After a response of 50-100%, the median levels of hemoglobin increased from 11 g/dL to 13 g/dL.

Clinical outcome

Among the 51 patients with a >25% decline in the myeloma protein, 10 showed disease recurrence. After a median follow-up of 8 months (range 3 to 16), the median time to progression was 12 months (Figure 1). The median overall survival was not reached and 91% of patients were alive.

Toxicity

Most adverse effects were recorded as grade I according to the World Health Organization toxicity classification. Thalidomide had to be discontinued because of toxicity in only 8 patients. Constipation was relatively frequent but well controlled with appropriate medication. Sedation was recorded in 6% of patients, changes in full-time or part-time working habits were required in 4% only. Weakness and fatigue were experienced in 8% of patients. These symptoms were drastically reduced when patients took thalidomide at dinnertime. Mood changes or depression were present in 4% of patients, but mainly in elderly subjects. Tingling and numbness were observed in an unexpected 14% of patients as grade I, in 3% as grade II. These symptoms developed after a median time of 3 months. Tingling required thalidomide discontinuation in 5% of patients, but 3% then experienced an improvement. Tremors and inco-ordination were present in 3% of patients and were generally mild. Dizziness was a late adverse effect (3%), and was mainly a clinical progression of foot numbness. One patient developed a severe skin rash on her face followed by vesicles and bullae: erysipelas was diagnosed and successfully treated with oral antibiotics. In another patient, a severe necrotic ulcer of the skull was observed. Two patients had evidence of hypothyroidism. Blood counts generally improved when disease response was achieved. Two patients showed an increase in creatinine levels. In one patient disease progression occurred with a slight increase in Bence Jones proteinuria accompanied by acute renal failure requiring dialysis. No concomitant nephrotoxic therapy was delivered in these subjects. Previously reported episodes of deep vein thrombosis were not observed (Table 3).[21]

Discussion

The association of low-dose thalidomide plus dexamethasone was highly effective in patients with relapsed or refractory myeloma: 41% showed a >50% decrease in myeloma protein. In most patients, the serological response was accompanied by a significant improvement of asthenia and bone pain, and a marked increase in hemoglobin levels. Oral melphalan and prednisone induced a tumor mass reduction >50% in only 20% of resistant/relapsing patients.[22] Our data clearly show that

Table 3. Toxicity.

	No. of patients	% of total
Tingling and numbness	13	17
Constipation	9	12
Weakness and fatigue	6	8
Sedation	5	6
Changes in work habit	3	4
Mood changes and depression	3	4
Tremor	2	3
Dizziness	2	3
Erysipela	2	3
Hypothyroidism	2	3
Renal toxicity	2	3
Toxicity that required discontinuation of treatment	8	10

low-dose thalidomide and dexamethasone have a true anti-tumor effect and that this is superior to that achieved by oral melphalan and prednisone.

Recent data suggest that thalidomide alone is active in 30-60% of patients with refractory/relapsed myeloma.[12,16,21,23,24] With doses ranging from 200 mg to 800 mg/day, side-effects were encountered in 10-50%.[12] In our study, adverse effects were recorded in 5-15%. In the escalating dose studies already performed, no relation between dose and response has been demonstrated.[12,21] In preliminary reports, a dose as low as 50 mg/day was claimed to be effective in myeloma patients.[25,26] In our series, median time to response was 4.2 months. This was longer than previously reported times, perhaps due to the lower dose of thalidomide.

The importance of glucocorticoids has been demonstrated by evaluating melphalan and prednisone administration in the primary management of myeloma. Survival time was found to correlate with the dose of prednisone and not with that of melphalan.[27] In refractory patients high doses of prednisone or dexamethasone may induce remission in a significant proportion of cases.[13,14]

Thalidomide and dexamethasone are a logical combination since they may differ in their action against myeloma. Thalidomide acts via adhesion molecule alteration, anti-angiogenesis and modulation of T-lymphocytes, whereas dexamethasone exerts its effect by inhibiting IL-6 production. *In vitro*, the addition of dexamethasone increased the inhibition of proliferation induced by thalidomide on myeloma cell lines by about 35%. Thalidomide induced apoptosis in cells resistant to dexamethasone, suggesting the potential utility of the combination of these two drugs.[16]

Here, we demonstrate that the combination of thalidomide at 100 mg/day plus dexamethasone at only 40 mg, 4 days each month, is an effective treatment against myeloma. At this dose dexamethasone alone cannot induce partial response in 40% of refractory patients. For these patients, 30% partial responses were recorded when dexamethasone was delivered at 40 mg but 12 days each month.[13] When thalidomide was administered alone at doses ranging from 200 mg to 800 mg partial responses were achieved in 25% of cases in one report[12] and 40% in another.[23]

In conclusion this study confirms previous findings showing that thalidomide is a new compound for the management of myeloma and is the first demonstration that low-dose thalidomide plus dexamethasone is an effective treatment for myeloma patients. The low-dose thalidomide schedule is very well tolerated and highly effective. Whether this efficacy is due to an additive or synergistic effect with dexamethasone is not clear.

Contributions and Acknowledgments

AnP conception, design, interpretation of data, drafting the article; LG, AB, PP SB, CR, ST analysis, interpretation of data, critical revision; EG, AP critical revision, important intellectual suggestions, final approval of the version to be submitted. MB conception, design, drafting the article, final approval of the version to be submitted.

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Disclosures

Conflict of interest: none.

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This manuscript was peer-reviewed by two external referees and by Prof. Jesús F. San Miguel, who acted as an Associate Editor. The final decision to accept this paper was taken jointly by Prof. San Miguel and the Editors. Manuscript received January 5, 2001; accepted March 8, 2001.

Potential implications for clinical practice

Low-dose thalidomide is well tolerated and highly effective on refractory myeloma. A significant proportion these patients benefit from this treatment as a salvage therapy postponing the delivery of chemotherapy.

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525 __ **|a** Supplements accompany some numbers.
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530 __ **|a** Also issued online.
533 __ **|a** Microfilm. **|m** v. 1 (1920)-31 (1948). **|b** [Bethesda, Md.] : **|c** National Library of Medicine, **|d** 1993. **|e** 22 microfilm reels : negative ; 35 mm.
546 __ **|a** Summaries in English, French, and German.
546 __ **|a** Vols. for <1999-> called International ed. and have all articles in English.
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EXHIBIT A5

SHORT SURVEY

Joint Bone Spine 2001 ; 68 : 582-7

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Thalidomide: new indications?

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Summary – Thalidomide, which was developed as a nonbarbiturate sedative agent, was taken off the market in 1961 after it was linked to a spate of major birth defects. Gradually, thalidomide was reintroduced for the treatment of a few skin diseases including leprous erythema nodosum, severe mucosal ulcers (e.g., associated with HIV infection or Behçet's disease), lymphocytic skin infiltrations, cutaneous lupus erythematosus, and chronic graft-versus-host disease. Recent reports of original pharmacological properties including modulation of cytokine production (mainly reduced TNF-α production) and inhibition of angiogenesis have led to the suggestion that thalidomide may be useful in some inflammatory and neoplastic conditions. Several open-label studies and case reports have described the effects of thalidomide in Crohn's disease, rheumatoid arthritis, ankylosing spondylarthritis, systemic sclerosis, and a few other systemic disorders. In these indications, minor but dose-limiting side effects were apparently common. Thalidomide analogs with better acceptability profiles are under evaluation. The anti-angiogenic effects of thalidomide may make this compound valuable as single-drug therapy or as an adjunct to chemotherapy in patients with cancer, particularly those with metastases or multiple myeloma. This possibility requires further evaluation.
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angiogenesis / myeloma / thalidomide / TNF-α

Thalidomide, a glutamic acid derivative, was synthesized in 1954 and marketed in 1957 in Europe as a nonbarbiturate sedative agent. The low toxicity of thalidomide, even in high dosages, and its fast action made it extremely popular, particularly among pregnant women [1, 2]. In 1961, thalidomide was withdrawn from the market after it produced severe birth defects, primarily phocomelia (underdevelopment of the proximal limb segments), in thousands of children.

Starting in 1964, use of thalidomide as a therapeutic agent was recommended again solely for the treatment of erythema nodosum leprosum, a condition in which it was dramatically effective. More recently, new indications have emerged, most notably in the field of dermatology. During the last few years, thalidomide has been found to exhibit original pharmacological properties, particularly immunomodulating and anti-angiogenic effects, which suggest possible usefulness in selected inflammatory and neoplastic diseases [3-5].

MECHANISMS OF ACTION

Thalidomide exhibits a wide range of biological properties including sedative anti-inflammatory, immunomodulating, and anti-angiogenic effects *(table I)*. The mechanisms underlying these effects are poorly understood [2, 6-8].

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Table I. Potential mechanisms of action of thalidomide [3, 7].

• Modulation of cytokine release	⇒ inhibition of TNF-α and, to a lesser extent, of IL-1, IL-6, and IL-8 ⇒ activation of IL-4, IL-5, and IL-10
• Effect on T lymphocytes	⇒ increased CD8+ T cell counts
• Inhibition of angiogenesis	⇒ VEGF, βFGF, etc.
• Modification of adhesion molecules	⇒ modification between tumor cells and stromal cells
• Inhibition of growth and survival of some cells, particularly tumor cells	

Sedative effect

The sedative properties of thalidomide are ascribed to its glutarimide ring, which makes its molecular structure similar to that of other hypnotic and sedative medications. Thalidomide may activate sleep centers. Neither disturbances in coordination nor respiratory depression occur. The mechanism of action is distinct from that of barbiturates.

Immunomodulating effect

Thalidomide seems to have both inhibitory effects and stimulating effects on many of the factors involved in the immune response.

Modulation of cytokine production

One of the main properties of thalidomide is decreased production of TNF-α by human monocytes related to degradation of the TNF-α messenger RNA without inhibition of protein synthesis [9, 10]. This effect has been confirmed by in vivo studies in patients with erythema nodosum leprosum, although the exact molecular mechanism remains unknown. However, the influence of thalidomide on TNF-α is complex: paradoxical effects have been observed in patients with conditions characterized by high TNF-α levels, and several studies have found that the effect of thalidomide can vary across cell types and inductor types, to the extent that in some cases TNF-α production is enhanced [2, 11]. The anti-TNF-α effect of thalidomide has prompted trials of the drug in numerous inflammatory diseases. This effect undoubtedly plays a role in the antitumor activity of thalidomide. Inhibition of TNF-α production seems related also to inhibition of the activation of nuclear factor κ B (NF-κ B), which is the transcription factor for TNF-α; this mechanism may involve inhibition of the enzyme NF-κ B kinase [7, 12]. Thalidomide may also inhibit the production of interleukin-6 (IL-6), IL-1, some chemokines, and IL-8 [13]. Finally, thalidomide inhibits the replication of the human immunodeficiency virus (HIV) in monocytes of infected patients, apparently by inhibiting TNF-α [2, 6].

Thalidomide can modulate T-cell cytokines. Here also, conflicting results have been published, with in some cases co-stimulation of T-cells [7] and in others inhibition of IL-2 and interferon γ production and, above all, enhancement of IL-4 and IL-5 production [2, 6, 8].

Effects on cells

Studies have consistently shown that thalidomide stimulates the CD8+ T-cell response relative to the CD4+ response, decreasing the CD4+/CD8 ratio. Furthermore, in vitro exposure of activated CD4+ T cells to thalidomide switches the Th1 response to a Th2 response, an effect that explains the above-described cytokine modulation, particularly the increase in IL-4 production [14, 15].

Anti-inflammatory effect

Thalidomide reduces the susceptibility of monocytes and polymorphonuclear cells to chemoattractants, decreases phagocytosis, and decreases production of superoxide and hydroxyl free radicals (an effect possibly involved in the genesis of birth defects) [6, 16].

Thalidomide may antagonize prostaglandins E2 and F2, histamine, serotonin, and acetylcholine, and may have a lysosomal membrane-stabilizing effect similar to that of glucocorticoids [6].

Angiogenesis-inhibiting effect

Thalidomide has been shown to inhibit angiogenesis. This property is independent from the effect on TNF-α and involves inhibition of vascular endothelial growth factor (VEGF) and beta fibroblast growth factor (βFGF) [17]. Thalidomide decreases the expression of aVβ3 integrin by endothelial cells and modulates the expression of adhesion molecules.

This anti-angiogenic activity (in combination with TNF-α inhibition) may explain the therapeutic effects of thalidomide in some inflammatory diseases and in malignant tumors. The inhibition of angiogenesis both causes hypoxia within the tumor and blocks adhesion of the tumor cells to the extracellular matrix, thus preventing metastatic dissemination [18]. Finally, together with the influence on free radical production, this anti-angiogenic activity may be involved in the teratogenic effect of thalidomide.

CURRENT THERAPEUTIC INDICATIONS

In France, thalidomide is available commercially as 50-mg capsules for oral use (Laboratoires Laphal) but has not received a license from the French Drug Agency: it is available only in hospital-based pharmacies, which require a prescription by a hospital-based physician and a temporary authorization for use delivered by the AFSSAPS. A non-nominal temporary authorization for use exists for five indications: – type II leprosy reaction, including erythema nodosum leprosum; – severe aphthous ulcerations, particularly in HIV-infected patients; in Behçet's disease, thalidomide improves the mucocutaneous lesions but has no effect on the systemic manifestations; – lymphocytic infiltration of the skin (Jessner-Kanoff disease); – cutaneous lupus erythematosus refractory to conventional treatments; and – chronic graft-versus-host reaction.

Thalidomide can be prescribed only through a restricted drug distribution program that includes special monitoring requirements (art. R. 5143-5-4 and R. 5143-5-5 of the French Public Health Code). The patient must first sign a treatment and birth-control consent form. In additional to the original prescription, there must be two copies. The starting dosage ranges across indications from 100 to 800 mg/d; the full dosage is reached gradually according to tolerability. The maintenance dose varies from 50 mg/d to 50 mg twice a week.

Placebo-controlled trials have confirmed the efficacy of thalidomide in erythema nodosum leprosum, severe aphthous ulcerations in patients with Behçet's disease, aphthous and gastrointestinal tract ulcerations in HIV-infected patients, and cutaneous lymphocytic infiltration.

In other indications, a nominal temporary authorization for use must be obtained. In the near future, however, a non-nominal temporary authorization will probably be granted for myeloma.

POTENTIAL NEW INDICATIONS

Dermatological and infectious diseases

As discussed above, the main current indications of thalidomide are dermatological conditions. Anecdotal case reports and uncontrolled clinical trials suggest that thalidomide may be effective in other cutaneous and/or infectious diseases, including prurigo, HIV-related Kaposi's sarcoma, wasting caused by the acquired immunodeficiency syndrome (AIDS), chronic or recurrent erythema multiforme, cutaneous sarcoidosis, cutaneous Langherans cell histiocytosis, pyoderma gangrenosum, intracranial abscesses, and tuberculous meningitis [2, 6].

Although toxic epidermal necrolysis (Lyell's syndrome) is associated with high TNF-α serum levels, thalidomide has been found to increase mortality in this condition [2, 6, 19].

Multiple myeloma and other hematological malignancies

Singhal et al. showed that thalidomide is effective in patients with advanced multiple myeloma [20]. They gave thalidomide as single-drug therapy to 84 patients with myeloma refractory to conventional treatments. Median treatment duration was 80 days. The dosage was 200 mg/d initially and was increased gradually up to 800 mg/d according to tolerability. A response, defined as an at least 25% reduction in the monoclonal component, was recorded in 32% of patients, an extremely encouraging result in this population with refractory disease. The monoclonal component reduction was detected within 2 months after treatment initiation and was accompanied with a decrease in the number of bone marrow plasma cells and an increase in the hemoglobin level.

Similar results have been obtained in very recent open-label studies in patients with refractory myeloma [21-24]. The beneficial effect is ascribable in large part to inhibition of angiogenesis [25]. These consistent results have recently prompted the initiation of clinical trials designed to evaluate the usefulness of thalidomide both in combination with conventional chemotherapy during first-line induction treatment and as single-drug maintenance therapy after aggressive autologous bone marrow transplantation-based management or in patients with no pain.

Promising data warranting phase II clinical trials have been reported in other hematological malignancies including myelodysplastic syndromes and myelofibrosis.

Solid malignancies

The key role of angiogenesis in malignant tumor growth, invasiveness, and metastatic dissemination raises the possibility that the anti-angiogenic effect of thalidomide may be beneficial in patients with malignant tumors. Promising results have been obtained in some forms of advanced cancer such as gliomas, prostate cancer, renal cancer, colorectal cancer, melanoma, and Kaposi's sarcoma, although no benefits have been reported in breast cancer or lung cancer [26-31].

A palliative effect of thalidomide on cancer-related constitutional symptoms (weight, appetite, sleep, night sweats) [32] has been noted with low dosages (100–200 mg/d).

Inflammatory diseases

The dramatic efficacy of TNF-α inhibitors in inflammatory diseases including Crohn's disease, rheumatoid arthritis, severe ankylosing spondylitis, and other connective tissue diseases has prompted open-label studies.

Crohn's disease and other inflammatory bowel diseases

Three open-label studies obtained encouraging results in about 50% of adults and children with severe Crohn's disease [33-36].

As mentioned above, thalidomide improves the gastrointestinal ulcerations related to HIV infection.

Rheumatoid arthritis

Rheumatoid arthritis (RA) has been shown to respond better to TNF-α inhibitors than to any of the conventional drugs. A few studies of thalidomide have been conducted in RA, using an open-label design. Surprisingly, they produced disappointing results.

The only study with positive results was reported by Gutierrez-Rodriguez et al. in 1999 [37]. In this open-label study, 17 RA patients were given thalidomide in an initial dosage of 300 mg/d, increased subsequently by 100-mg steps according to tolerability. Mean dosage was 531 ± 63 mg/d. After a mean treatment duration of 18.8 ± 8.8 weeks, 12 patients were in complete or partial remission. Furthermore, decreases occurred in the erythrocyte sedimentation rate and rheumatoid factor titer.

More recently, Huizinga et al. reported an open-label study in which 12 patients with active RA took 1200 mg of pentoxyfylline and 100 mg of thalidomide per day in addition to their usual treatment [38]. Nine patients completed the study and five met American College of Rheumatology 20% response criteria.

Scoville conducted an open-label trial of thalidomide in 25 RA patients [39]. Various dosages were used. Nine patients discontinued treatment because of side effects, seven responded to dosages greater than 300 mg/d, and five failed to respond to dosages lower than 200 mg/d.

Keezal et al. used thalidomide in ten patients with active RA who had discontinued their conventional second-line drugs at least 1 month earlier [40]. The dosage was 100 mg/day for 4 days with subsequent increments of 100 mg at 4-day intervals. Side effects prevented eight of the ten patients from increasing the dosage beyond 200 mg/d. None of the clinical or laboratory test parameters improved. Note, however, that only three patients completed the 16-week study period.

Finally, a recent report suggests that thalidomide may be useful in combination with methotrexate in patients with rheumatoid arthritis [41].

Ankylosing spondylitis

Two HLA B27-positive patients with refractory ankylosing spondylitis were given thalidomide in a starting dosage of 100 mg/day increased gradually to 300 mg/d then continued for 6 months in a maintenance dosage of 200 mg/d [42]. Prompt improvements were recorded in clinical parameters (BASDAI and BAFI) and laboratory tests (erythrocyte sedimentation rate and C-reactive protein) in both patients. One of the patients relapsed shortly after discontinuation of the drug. Several similar cases have been reported recently.

Other inflammatory diseases

In lupus, thalidomide often produces marked improvements in refractory cutaneous lesions but fails to noticeably improve joint and systemic manifestations [2, 6, 43]. Similarly, the beneficial effects of thalidomide in Behçet's disease and sarcoidosis are confined to the skin lesions.

In patients with systemic sclerosis, promising improvements in clinical and laboratory test abnormalities have been obtained, and anecdotal evidence of effectiveness has been reported in patients with Still's disease or Sjögren's syndrome [44].

CURRENT LIMITATIONS TO THE USE OF THALIDOMIDE AND FUTURE PROSPECTS

Apart from dermatological and infectious diseases, thalidomide may be indicated as single-drug or adjuvant therapy in patients with multiple myeloma, some forms of solid cancer, and some inflammatory conditions producing articular, gastrointestinal, or systemic manifestations. The efficacy of thalidomide needs to be confirmed by randomized clinical trials. However, the main limitation to thalidomide treatment seems to be the common occurrence of dose-limiting side effects [4, 39].

Side effects are common [2, 6, 19]

The ability to induce birth defects is, of course, the best-known side effect of thalidomide. The mean rate of occurrence may be about 30%. The limbs and most organs can be affected. Effective contraception and regular hormonal testing are essential in women of childbearing potential. Whether thalidomide can induce birth defects when given to men is not agreed on; in France, patients are advised to refrain from possibly procreative sexual intercourse throughout treatment and during the first 3 months after treatment discontinuation. However, thalidomide seems devoid of mutagenic effects.

Peripheral neuropathy is the main problem. The neuropathy is axonal and predominantly affects the sensory fibers, in a bilateral symmetric distribution. The neurological loss starts at the hands and feet. Because this complication is common, neurological examinations and electromyograms should be obtained at regular intervals.

The other side effects are not serious but can be so intense as to be dose-limiting. They consist mainly of malaise, drowsiness (45–90% of patients), asthenia, vertigo, headache, constipation, nausea, dry mouth, dysesthesia, fever, skin lesions, sphincter dysfunction, tremor, and amenorrhea.

Recently, more severe cases of toxic skin involvement have been reported, with in particular one case of toxic epidermal necrolysis. An increase in the risk of venous thrombosis has been reported in patients with multiple myeloma.

Thalidomide analogs

These side effects of thalidomide have prompted efforts to develop analogs with greater anti-TNF-α activity but less toxicity. Two groups of analogs have been obtained, IMiDs and SelCiDs. The difference between these two groups lies in the ability to inhibit the enzyme phosphodiesterase type IV [7, 8]. Promising results have been obtained in animal models, but no data are available in humans.

In conclusion, thalidomide exhibits exciting biological properties dominated by inhibition of TNF-α production and inhibition of angiogenesis. These properties have prompted evaluations of thalidomide in several dermatological and infectious diseases and, more recently, in inflammatory and malignant conditions including myeloma and some solid cancers. Additional clinical studies are needed to confirm the efficacy of thalidomide, to determine its optimal dosage, and to define its place in the therapeutic strategy for these conditions. In inflammatory diseases, particularly those affecting the joints, the risk/benefit ratio does not seem favorable given that specific TNF-α inhibitors are now available.

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