The Successful Implant: Ensuring Safety and Performance of Medical Devices

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Microscopic evaluation, and occasionally ultrastructural evaluation, are used to document morphologic findings in tissues that are associated with medical devices (Alves et al, 2012). Morphologic findings help to understand safety (biocompatibility), performance (function), and efficacy (capacity to treat or prevent disease) of new medical devices or of drug-eluting medical devices (combination products) at both the tissue and cellular levels. Microscopic evaluation of safety has a central position in regulatory testing programs (ISO 10993, ASTM International, EMEA guidance documents, FDA recommendations). The standard ISO 10993 – Part 6 is specific to the testing and evaluation of local effects on soft or hard tissues in contact with an implant, whereas the systemic effects of implants are covered by the ISO 10993 standard – Part 11.

For both safety and performance, non-clinical and clinical evaluation of implanted test articles requires the examiner to have a basic understanding of materials science, bioengineering, and pathobiology. Although microscopic evaluations, and less frequently ultrastructural evaluations, are routinely employed in the assessment of implants, specific techniques are used to help understand both the implant’s performance itself and the host’s response to implantation. These include the following:

1. The use of imaging techniques that allow for continuous follow-up of the behavior of the implant and host response in testing models, both live and following euthanasia.

2. The development of quantitative criteria to characterize the descriptive pathology.

3. The integration of computer-assisted analysis, allowing image analysis using morphometric criteria, large fields reconstitution, and statistical comparisons of objective criteria.

The understanding of the complex reactions involving specific implant characteristics (chemical, physical, and thermal), as well as cellular and secretory factors, collectively determines success or failure of medical devices. Understanding molecular, cellular, tissue, and organ pathobiology, in addition to the principles of healing, is essential for evaluating the local implant or tissue interface and potential systemic effects on the host. Selection of the host testing model, surgical technique, healing time, clinical endpoint, technique for specimen preparation, and finally morphologic (microscopic and ultrastructural) criteria are pivotal in the evaluation of the implant and host response. These criteria have to be adapted specifically for each device or biomaterial. As for the full testing program of biocompatibility, it is advised that these microscopic and ultrastructural investigations be conducted under Good Laboratory Practices or under an ISO 17025 quality system to ensure competent, reliable, and independent analysis of the implant/host response.

The safety assessment of medical devices is complicated by the diversity of devices and components, but also by the variety of clinical indications for these devices. Here we discuss commonly used and innovative methods for investigating and interpreting implant and host response.
Local and Systemic Effects

**General Considerations for Evaluating Implant Histology**

Evaluation of tissue sections using a light microscope is still one of the most important and widely used techniques for defining tissue responses to biomaterials, both at the tissue/implant interface (local effects) and in distant tissues or organs (systemic effects). Specific recommendations for testing model selection and study design are detailed in various regulatory and guidance documents. Every effort should be made to mimic the intended clinical use of the test device or biomaterial. For example, vascular devices should be tested using intravascular implantation, materials intended for mucosal application should be tested using mucosal (oral, rectal, vaginal) exposure, and materials or devices for intra-abdominal use should be implanted to allow the evaluation of peritoneal or serosal reactions. In specific instances, it may be appropriate to stress the test system to simulate adverse clinical events; for example, it may be appropriate to use skin-wound models when testing products intended for topical application, thereby evaluating effects on dermal and subcutaneous tissue should the epidermal barrier be breached.

During the histotechnological treatment of organs to determine if any particular organ was affected by the implant, it is recommended to follow the guidelines proposed by the Registry of Industrial Toxicology Animal-data (RITA) procedures. The intent of the RITA procedures is to provide standardized sectioning of tissues and to optimize the comparability and interpretation of biological responses across treatment groups and among laboratories. The preparation of implant or injection sites for microscopic evaluation is dependent on the density and hardness of the implanted material. For example, dense or hard materials will likely require plastic embedding for sectioning or preparation by grinding, while soft tissues embedded in paraffin and stained are suitable for morphologic evaluation in screening for systemic effects. Adverse local cellular or tissue effects may be due to toxicity or immunological responses associated with the implant, implant degradation products, or leachable components.
Case Study: Challenges in Assessing Ocular Medical Device Interaction With the Eye

In general, ocular medical devices are tested for evidence of biocompatibility (ie, absence of localized irritation or toxicity), but if the ocular device elutes a drug, then additional organs and tissues in the body are often evaluated for systemic toxicity. Ocular medical devices include those that come in contact with either the exterior of the eye (eg, contact lenses and nasal canalicular plugs) and those that are implanted within structures of the eye globe (eg, intraocular lenses and intravitreal implants). For ocular devices, regardless of the host used, during regulatory submission the examiner needs to be aware of the ocular structures and spontaneous background findings that are uniquely associated with a particular host, as well as the general responses of ocular structures to physical or chemical injury, in order to determine if microscopic ocular findings are of toxicological importance.
Considerations for Evaluating Ocular Medical Devices

Evaluation of ocular medical devices generally involves an in-life phase in which ophthalmic examinations are performed using one or more clinical methods, such as direct ophthalmoscopy, indirect ophthalmoscopy, slit-lamp biomicroscopy, tonometry, electroretinography, or optical coherence tomography, to mention a few. Microscopic ocular findings need to be correlated to clinical ocular findings; therefore, globes are generally handled separately from the other tissues to minimize artifacts (Weir and Collins, 2013). The postmortem phase involves careful handling during enucleation, maintaining identification (right or left) and orientation of the globes, use of special fixatives that minimize artifacts, trimming the globes in a uniform manner that ensures that the ocular structures of interest will be in the plane of section, and care at the time of embedding in paraffin blocks. Special procedures may be incorporated into an ocular protocol to ensure that the eye is adequately examined.

Key Considerations for Systemic Effects

Systemic effects are defined as “those effects occurring in tissues distant from the site of contact between the body and the medical device or biomaterial.” Systemic effects can be associated with leachable chemicals or degradation products released from a medical device following exposure to biological fluids, inflammatory cells, or both. Mechanisms associated with systemic effects include: chemical toxicity, non-specific cytokine activation with systemic inflammation, vasoactive effects associated with complement activation, or a specific immune-mediated response. Acute toxicity refers to adverse effects occurring within 24 hours following exposure to the implant. The evaluation of acute toxicity is based primarily on clinical observation, and microscopic examination of tissues is less commonly performed.

Microscopic evaluation of tissues is an important endpoint in assessing subacute (24 hours–28 days), subchronic (typically 3 months in rodents) or chronic (6–12 months) systemic toxicity following repeated or continuous exposure to an intact device or its components. Recommendations regarding the specific tissues to be
evaluated are provided in guidance documents, but should include at minimum tissues representative of major organ systems: liver, spleen, thymus, kidney, adrenals, lymph nodes, heart, lung, and testes or ovaries. Additional tissues (eg, brain, spinal cord, peripheral nerve, pituitary, thyroid, and reproductive tract) should be included to address specific concerns relative to neurotoxicity, endocrine effects, and reproductive effects, respectively. Microscopic evaluation of tissues for alterations indicative of systemic effects requires adequate knowledge of normal anatomy and incidental background changes in the host being used. The interpretation of microscopic findings requires thorough correlation with clinical observations, clinical pathology (hematology and clinical chemistry) data, organ weights, and macroscopic changes noted at necropsy. When needed, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) should be used for analysis at the ultrastructural level to further refine the safety evaluation, for instance following testing the effects of nanomaterials.

Performance Evaluation

Evaluation of performance starts with macroscopic observations of implanted sites. Gross findings are best reported in a purely descriptive manner. Macroscopic scoring of the implant performance is recommended, based on available standards or scientific literature. Data from clinical techniques such as radiography, magnetic resonance imaging (MRI), ultrasonography, computerized tomography (CT), micro-CT (μCT), ocular imaging (eg, optical coherence tomography), and other imaging techniques used for implanted sites are valuable in completing the macroscopic and microscopic analyses of performance. In bone tissue, signs of stress are not observable on the histological slides when the sampling is restricted to the implant interface. In this case, imaging results, along with the microscopic observations, provide a more insightful analysis of the implant performance. Three-dimensional representations of the implanted sites obtained with tomographic tools enrich the interpretation of implant performance and may help to determine the most relevant plane of histological section.

Structural characteristics of the non-implanted devices are used to describe the in vivo behavior of the implanted materials. Signs of material changes such as erosion, swelling, creep flow, cracks, fragmentation, delamination, or breakdown will invariably impact the host tissue response. Therefore, the description of material changes should be included as part of the tissue response analysis. Staining of un-implanted material that is processed, embedded, and stained under the same conditions as for the treated sites, will serve as baseline control. Special staining techniques can be used for the detection of specific tissues, cells, or implant components, or to detect activity in the tissues or cells surrounding the implant. These special staining techniques include histochemistry, enzyme histochemistry, immunohistochemistry, and molecular histology.
Quantitative Pathology

Quantitative histomorphometric evaluation is primarily used for performance characterization but can serve for safety issues. Examples include the measurement of inflammatory cellularity following marking of specific inflammatory cells or evaluation of local cytokine expression. Computer-assisted quantitative histomorphometry, rather than a qualitative or semi-quantitative analysis, is an appropriate way to evaluate and compare materials, reactions, and reconstitution of tissues or organs, whenever performance evaluation is conducted. This method permits measurement of morphologic characteristics of tissue reactions such as infiltrating cells and extracellular material/components, as well as the implant material itself. These techniques provide accurate and objective metrics allowing statistical comparison between implant treatments. In dental, bone (cranio-maxillofacial, vertebral, long, cortical, trabecular, or ectopic), and vascular healing, quantitative approaches by histomorphometry are commonly used. Fine comparison and powerful discrimination between test and control implants are established when close peri-implant tissues and implant measurements are carried out. The time course of healing or material changes such as degradation can be quantitatively characterized by this method.

For evaluation of bone implants or bone substitutes, a commonly used parameter is the bone-to-implant contact percent (BIC %), which reflects the level of osteointegration and osteoconduction at the surface of implants. In addition, bone area density is a useful parameter that often correlates well with material degradation, thus allowing the qualification of an implant as being a bone substitute. By the means of histomorphometry, the osteotransduction process (material replacement by a newly formed bone) is characterizable. In vascular treatment, a sensitive parameter is thickening of neointimal tissue. Measurement of neointimal hyperplasia indicates the effect and performance of an endovascular implant on the prevention of vascular re-stenosis. In general, computational histomorphometric approaches are less often applied in soft tissue repair than in hard tissues. However, we recently developed an approach for the quantitative evaluation of soft tissue repair by measuring the speed of implant integration into soft tissues (manuscript in preparation). Using two specific staining methods (Picrosirius Red for collagen determination and Feulgen and Rossenbeck for DNA staining), the extracellular matrix and the cellularity were respectively measured within abdominal reinforcement meshes to provide a value of the rate of tissue (cells and collagen) ingrowth over time.

Conclusion

With the variable biomaterials used for implantable medical devices, it is important to choose the best approach to evaluate each one. On the other side, the use of imaging techniques in live testing models will allow reconstruction of a full device–host interaction and complement the microscopic description of the different events.
A wide range of interactions occurs between living tissues and biomaterials. Beneficial or adverse effects may be observed. Microscopic examination of implanted sites is one of the most important methods for the assessment of cellular and extracellular events that comprise the host response, and is important in determining if and what additional testing is necessary. Minimal local biological response does not negate the potential for systemic effects (e.g., endovascular device and thromboembolism, toxicity associated with leachable components). A harmonious implant-tissue interaction can convert into an undesirable reaction due to material changes over time in a given biological environment. A deleterious local reaction to an implant does not necessarily mean that the implant is not qualified. Immune reactions linked to the host used can result in xenogenic reactions and may require the use of immunodeficient testing models to better define tissue reactions.

The ability of a material to perform with an appropriate host response in a specific situation defines the term of biocompatibility. Hence, microscopic evaluation of safety and performance is interdependent and complementary. That is why the description and the grading of safety findings, as defined for example by the ISO 10993-6, should develop in a direction that takes into account performance criteria, yet still remains part of the safety evaluation. For example, a biotextile designed for tissue reinforcement can elicit a minimal tissue reaction without significant signs of tissue ingrowth, which corresponds to suboptimal implant performance and an unsafe medical device. Microscopic quantification of safety and performance findings is one of the most challenging aspects for the future, particularly with regard to soft tissues. The use of new microscopic techniques, such as digital pathology and quantitative imaging, will contribute to integrating information on safety and performance of implants. This new perspective should help in achieving a more accurate microscopic assessment and in understanding the host response to implanted medical devices.

References
