I.D.A.C. Report Summary

Project ID: 277988
Funded under: FP7-HEALTH
Country: Italy


Executive Summary:
With a share of 38%, orthopaedic and traumatology (O&T) are the worldwide leading markets of implanted biomaterials, involving millions of new patients each year at an increasing trend. Infection related to implanted medical devices is directly related to bacterial capability to establish multilayered, highly structured biofilms on artificial surfaces. Bacterial infections due to implanted biomaterials represent the most devastating complication in O&T, involving millions of European citizens.

Aim of IDAC was to develop, validate and bring to the market a disposable coating of implanted biomaterial (Implant Disposable Antibacterial Coating, I.D.A.C.). The device, based on a novel, proprietary, resorbable hydrogel, acts as a fast resorbable local delivery carrier of antibiofilm and antibacterial compounds. The active drug (antibiofilm and antibiotic agents) is mixed at the time of the hydrogel application, allowing the correct choice for any given patient, reducing regulatory requirements, improving storage life and versatility. In particular, I.D.A.C. has been tested as a resorbable carrier of drugs (e.g.: N-acetylcisteine and its derivatives, serratia peptidase and other peptides, etc.) already known from our studies for having excellent antibiofilm properties, while others are able to by-pass the intact biofilm barrier and kill the underlying bacteria, when locally administered.

The final purpose of this research was to set a novel approach to early control of biofilm formation, to prevent bacterial colonization of implanted material and to treat established implant-related infections and chronic wounds, without any risk of inducing new drug resistance and alter the environment.

The research has been conducted under the aegis of the European Bone and Joint Infection Society and the European Hip Society, through a network of upper standard European research and clinical centers and experienced SMEs from eight Countries around Europe.

Project Context and Objectives:
The aim of the present research was to develop, validate and bring to the market a fast resorbable, disposable anti-biofilm and anti-bacterial coating of implanted biomaterials (I.D.A.C. Implant Disposable Antibacterial Coating), to be used in O&T. I.D.A.C. is based on a recently patented (from CO1-Novagenit, patent no. WO2010/086421 A1) fast resorbable, biocompatible hydrogel, obtained from derivatives of hyaluronic acid and other biocompatible polymers; I.D.A.C. was designed to be intraoperatively loaded with antibiotic/antibiofilm agents and used for antibacterial coating of prostheses and other implanted materials in O&T. I.D.A.C. represents a novel approach to early control biofilm formation, prevent bacterial colonization without any risk of inducing new drug resistance and alter the environment.

According to the original concept of (i) winning the “race to the surface”, before bacteria replication and biofilm production take place on the implant surface; (ii) providing a local protection through high local antibiofilm/antibacterial compounds concentrations and (iii) with a fast and complete resorption of the coating within the first days after surgery, I.D.A.C. has demonstrated to defend the implanted biomaterials.
Novelty, versatility, ease-of-use, efficacy, safety and reduced costs are the key-factors for the success of the present idea. More specifically, the project developed and validated this novel tool, with particular reference to:

Objective 1: To develop and test the ability of the patented hydrogel to deliver known and new antibiofilm compounds and antibacterial agents. Shelf-life and sterilization procedures was also investigated as a part of this objective.

Objective 2: To develop and test the ability of the technology under study to prevent early bacterial colonization and biofilm formation on implanted biomaterials in vivo.

Objective 3: To test the ability of I.D.A.C. to disrupt biofilms once established, and decrease infection rates in contaminated or infected implants, from different microorganisms.

Objective 4: To test the hydrogel resorption within a pre-defined, controlled period of time (target: 96 hours), avoiding the risk of delayed unwanted side effects or interference with osteointegration of the implant.

Objective 5: To develop and test a simple tool for intra-operative mixing of the hydrogel with the selected antibiofilm/antibacterial compounds and to test in vivo the best procedure to achieve a complete coating of the implant.

Objective 6: To assess safety, efficacy and ease-of-use in the clinical setting. Two clinical trials were performed in the second part of this collaborative research project.

**Project Results:**

During the time period starting from Jan 2012 to June 2015, the following activities were performed by the partners involved in the project:

1. Development and testing of a fully biocompatible hydrogel, able to meet all ISO standards and to be loaded with various antibacterials;
2. Demonstration of the antibacterial and antibiofilm activity of the hydrogel alone or in combination with various antibacterial compounds;
3. Demonstration that the hydrogel can be applied as an anti-bacterial coating in metallic (titanium alloy and cobalt chrome) and non-metallic (polyethylene) biomaterials;
4. Demonstration that the hydrogel can be stored for up to 2 years at refrigerated conditions as a powder in a prefilled syringe;
5. Development of a kit to mix the hydrogel with an anti-bacterial at the time of surgery;
6. Further improvement of said kit in order to allow intra-operative spreading of the hydrogel on an implant;
7. Demonstration that the hydrogel, applied as a coating of an orthopaedic implant, is capable to resist press-fit insertion without declothing of the implant;
8. Demonstration of the anti-bacterial and antibiofilm activity of the antibiotic-loaded hydrogel applied on different biomaterials;
9. Demonstration of the safety of the antibiotic-loaded hydrogel in an animal model of implant-related infection;
10. Demonstration of the antibacterial efficacy in an animal model of implant-related infection;
11. Demonstration of the safety of the antibiotic-loaded hydrogel in a multi-center trial on hip and knee joint prosthesis;
12. Demonstration of the safety of the antibiotic-loaded hydrogel in a multi-center trial on osteosynthesis for closed fracture;
13. Dissemination of results in national and international invited lectures, podium presentations and posters;
14. Dissemination of results through scientific peer-reviewed journals, the internet and the mass-media (press and TV release);
15. Market analysis concerning the picture and the trend of orthopaedic implants in 5 European Countries, the competitors and current technologies in the field of antibacterial coatings of biomaterials;
16. Trademark registration and CE mark achievement of the final product.

Here below a summary of the activities and results for each Workpackage is presented.

**WP1 Prototypes development and laboratory testing.** The characterization of powder and hydrogel form was performed. Evaluation of anti-biofilm activity of hydrogel reconstituted with (i) bioactive glass powder (no negative influence on bioactivity of glass. IDAC does not interfere the BAG pH increase (reason for the bacterial growth inhibiting BAG effect); (ii) gentamycin, vancomycin and N-acetylcycteine (NAC) (greater anti-biofilm and anti-bacterial activity against Staphilococcus aureus and Staphillococcus epidermidis than each substance tested alone including hydrogel. Clear impact of the material on biofilm
formation observed). Tobramycin, amikacin: all real curves fit more or less to the theoretical one. Diclofenac was efficient with 4 and 20 mg/ml. Furanone did not inhibit biofilm formation in concentrations water-soluble. Daptomycin, ciprofloxacin, meropenem inhibited biofilm formation.

Different batches of IDAC powder resulted sterile in all cases and with endotoxin levels < to 0.125 EU/item. Sterilization procedure was performed with beta irradiation at 22kGy without any modification on the batches release kinetic. Shelf life: 6 months at +25°C corresponding to 24 months at refrigerated conditions.

WP2 Post prototype laboratory testing. Drag test (on human cadaveric femur and rabbit tibia) has been successful both with and without vancomycin addition to the hydrogel: after implantation, there is complete adhesion of hydrogel to prosthesis surface. All the biocompatibility studies required by the ISO 10993-1 were carried out successfully. The mixing/spreading operations received full approval. A pilot study in 9 rabbits was performed for determining the bacterial doses to be used in the animal experiment. It was decided to inoculate 105 CFU of Staphylolcoccus aureus. A large animal study (60 rabbits inoculated with 105 CFU) was performed to test the efficacy of different antibiotic and anti-biofilm agents loaded in IDAC gel. The vancomycin-containing iDAC hydrogels, both 2% and 5%, successfully prevented local infection around the implant after contamination of the implant bed.

In the groups Gel + Bioactive Glass and Gel + NAC (N-acetyl cysteine) the infection was not prevented.

A further study (18 rabbits) was successfully carried out without bacteria inoculum to demonstrate that the IDAC hydrogel, alone or in combination with vancomycin, did not have any influence on inflammation or bone formation.

Moreover, in deep testing of further microbiological activities on multi-resistant and on strong biofilm producer bacterial strains of the I.D.A.C. hydrogel combinations have been conducted.

WP3 Human testing. The documents (protocols, Informed Consent Form, Case Report Form) related to the clinical trials (infection prevention in total hip/knee arthroplasty, and in traumatology) were prepared and provided for the submission to the Ethical Committees. The safety, the efficacy and the easy-to-use were tested in 2 different clinical settings (hip/knee joint replacement and osteosynthesis). The local Ethical Committee approvals were obtained by all centers (IT, EL, BE, A). The patients enrolment has been concluded and the planned 12-months follow up is ongoing. The preliminary results show the safety and efficacy of the product: none Intra-operative complications related to the investigational product was reported; none immediately post-operative complications related to the investigational product was reported.

WP4 Data analysis. The procedure for centralized data collection/processing was provided and central database were developed. The central database was managed and updated with data resulting from WP1, 2 and 3. A preliminary statistical analysis based on WP3 data entered was performed.

WP5 Management. Organisation of internal meetings and conference calls, collection of financial and technical data for the preparation of the periodic / final reports, deliverables submission and achievements of milestones, preparation of project amendments.

WP6 Dissemination and Exploitation. Creation and update of project website, dissemination of the project results through oral presentations and posters, articles in peer-reviewed journals, organisation of two IDAC meetings, release of interviews to popular press and TV news. A market analysis was carried out regarding the status quo and the trend of orthopaedic implants. The optimization, the standardization and the validation of the manufacturing process for IDAC product was carried out with success.

Potential Impact:
IDAC has provided a new tool for biofilm formation prevention and biofilm disruption in orthopaedic and traumatology, the largest market for implanted materials (currently accounting for 38% of the whole market of implanted biomaterials worldwide). It represents the first, new approach to the severe and growing social and economic burden of implant-related infections in O&T. IDAC is expected to provide a novel approach to the containment and treatment of nosocomial implant-related infections, through local, fast, complete delivery of anti-bacterial/anti-biofilm agents.

Until now chemotherapy of implant-related infection is rather exclusively based on systemic administration of antibiotic and implant removal is often necessary to eradicate infection.

Systemically administered antibiotics suffer the limit of questionable penetration into biofilms and at bone-implant interface, require prolonged therapy at high doses and are often associated with limited efficacy, induced resistance, unwanted side
effects and high costs.

The IDAC consortium has provided clear evidence of: a) efficacy: in vitro and in vivo demonstration of the antibiofilm/antimicrobial properties of IDAC and its ability to protect an implant from bacterial colonization; b) safety: due to the complete/fast delivery of the antibiofilm/antibacterial compounds and resorption of the hydrogel; c) ease of use: intra-operative use of IDAC requires only few minutes, without any particular training of the surgeon/nurse; d) reasonable costs: the product appears to have an attractive economic margin. IDAC is CE marked (July 2013).

No direct competitors are available on the international market and the marketing opportunities grow due to the increase of medical devices implanted for more pathologies, trauma and particularly due to the progressively ageing population and its better quality of life. General trend of growth for the European orthopaedics implants market (from 2,5 to 4% /year). The treatment of each new peri-prosthetic infection accounts for an estimated cost of Euros 60.000 to 80.000. Septic prosthetic revision represents 2 to 3 times the cost of an aseptic revision and 4 to 5 times the cost of a primary surgery. Revision surgery and compromised hosts (diabetic, smokers etc.) present an higher incidence of septic complications.

For the patient, the impact is heavy, as it includes: loss of autonomy and sometimes residual disability (up to amputation), work stoppage and often loss of wages, negative psychological impact associated with a new longer and unwanted surgery in contrast to the first scheduled replacement.

IDAC, is also expected to have a relevant impact on social and medico-legal issues. While all indicators show the success of joint replacements and a sustained increase of the number of joint implant performed annually throughout in Europe and worldwide, postsurgical septic complications still bring an extremely high toll in social terms, as to regard work inability, quality of life reduction and long term treatments needed. Introducing a new tool for implant-related infection prevention would benefit hundreds of thousands of European citizens and save a considerable amount of money from direct and indirect costs.

Medico-legal claims following nosocomial infections are growing fast, at least in some European Countries, raising concerns as to regard the ability of surgeons and hospitals to sustain the cost of the risk in the next years. Any simple and effective procedure available would be immediately introduced in the clinical use and meet patient’s, surgeon’s and hospital’s needs and expectations, reducing claims and litigations. IDAC can easily enter in the strategy of European Health policies in the fight against bone infections. The technology may be transferred to other potential markets (spine surgery, dental surgery, maxillofacial/plastic surgery, chronic wound management, war surgery in countries with high risk of infection etc.).

List of Websites:

www.i-dac.eu

Related information

| Result In Brief | Bacteria-proof resorbable implant coating for orthopaedics |

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Last updated on 2015-12-22
Retrieved on 2019-07-30
