(54) Title: ABSORBABLE PATCH IN PGA FOR THE REPLACEMENT OF A PORTION OF BLADDER WALL FOLLOWING PARTIAL CYSTECTOMY

(57) Abstract: A description is given of a patch (200) for the replacement of a portion of bladder wall, following partial cystectomy, comprising a textured textile (2) deriving from a yarn of PGA and provided with one or more reinforcement strips (30) made up of the same textured textile (2) and positioned on the lower surface (4) of said patch.
ABSORBABLE PATCH IN PGA FOR THE REPLACEMENT OF A PORTION OF BLADDER WALL FOLLOWING PARTIAL CYSTECTOMY

DESCRIPTION

The present invention relates to an absorbable patch for the replacement of a portion of bladder wall, following partial cystectomy.

As is known, when a portion of the bladder of a patient is affected by a serious pathology such as partial neoplasia or bilharzia (schistosomiasis), this portion of bladder has to be removed to prevent the pathology from spreading to the whole bladder. Removal of this portion of bladder creates a hole in the bladder which is closed using a patch which is sutured to the perimeter of the bladder wall which defines this hole.

The patches are generally made up of tissue taken from the reversed intestine of the patient or of synthetic materials, for example silicone or material in polypropylene as described in the patent applications WO 2007/039160 and PCT/EP2008/006352 in the name of the Applicant, which are rendered more biocompatible by covering with a layer of turbostratic pyrolytic carbon or of fatty acids of the omega-3 family.

Some of these patches serve to replace temporarily the part of bladder removed while awaiting the regeneration of the bladder tissues around the hole and therefore have to be removed endoscopically at a later time by subsequent further surgery on a day hospital basis. This operation however is not always easy to perform, in particular on elderly patients.

Moreover these patches must have a combination of properties which cannot always be achieved by known natural or synthetic patches: a rigidity such as to allow the bladder to retain its shape at least until its removal, and at the same time adequate elasticity and flexibility such as to ensure the correct deformation of the patch during the natural functioning of the bladder whereon it is applied.

Additionally the patch has to demonstrate a chemical resistance and impermeability to urine at least for the entire period from engrafting until its removal, or absorption.

Moreover said patch must not collapse under the weight of the growing tissues, which is
instead a typical phenomenon of flexible three-dimensional matrices of small thickness, nor demonstrate any adherences to the surrounding fibrotic capsule.

An alternative solution to the aforementioned non-absorbable patches is represented by the use of three-dimensional matrices, generally in bioabsorbable material, which act as substrate (scaffold) for growing in vitro stem cells of the diseased organ in order to obtain a piece of biological tissue which will then be implanted in place of the portion of diseased tissue. This procedure allows excellent results to be obtained in terms of compatibility and mechanical performances yet is more complicated, with long performance times, and costly.

The object of the present invention is to eliminate the disadvantages of the prior art, providing a patch for the replacement of a portion of bladder wall, following partial cystectomy, which does not require a subsequent surgical operation for its removal.

Another object of the present invention is to provide such a patch which is also practical for the surgeon and at the same time simple and fast to make.

Yet another object of the present invention is to provide such a patch which is reliable, particularly as regards the impermeability and resistance to urine, which does not swell up once implanted and which has good mechanical strength, in particular which does not demonstrate collapsibility as the cell tissues grow, in order to ensure good performances of deformation of the bladder during its functioning, and which does not negatively influence the growth of the new biological wall tissue of the portion of bladder removed and does not adhere to the fibrotic capsule.

These objects are achieved by the patch in accordance with the invention having the features listed in the annexed independent claim 1.

Advantageous embodiments of the invention are disclosed by the dependent claims.

The patch according to the invention, for the replacement of a portion of bladder wall following partial cystectomy, comprises an absorbable (bioabsorbable) material and is in the form of a textile designed to ensure correct deformation of the bladder whereeto the patch is applied. Said textile is made using a yarn, multifilament or an ultra-lightweight monofilament, derived from fibres of a particular bioabsorbable (or absorbable or
biodegradable) polymer such as PGA (polyglycolide or polyglycolic acid), preferably homopolymer.

Moreover said patch is preferably provided with one or more reinforcement strips on at least one of its surfaces, made with the same type of textile as the patch.

PGA is a thermoplastic and biodegradable polymer, the simplest member of the family of linear aliphatic polyesters, and is characterised by a high degree of crystallinity, around 45-55% in the case of the homopolymer. PGA is hydrolytically unstable due to the presence of a series of ester bonds in its polymeric structure and, when exposed to physiological conditions, it degrades due to processes of random hydrolysis and also due to some classes of enzymes, particularly belonging to the family of esterases. Despite this, this material is particularly suited not to deteriorate in contact with urine for a period of at least two months,

The product of degradation of PGA is glycolic acid which is not toxic and can enter the Krebs cycle, at the end of which it is secreted in the form of water and carbon dioxide. A part of the glycolic acid is also eliminated in the form of urine.

PGA moreover has a degradation time which ranges from 4-6 months, even reaching 12 months, but it starts to lose its mechanical strength already after 4 weeks and it is completely lost at the fifth month. This however is compatible with the cell growth of the tissues of the bladder.

The fibres of PGA preferred for making the textile of the present patch are made of homopolymer since they appear very rigid and are characterised by a high tensile modulus value of 7 GPa and a minimum tensile strength of at least 4.5 grams/deniers. Thanks to these properties the textile obtained with the use of said fibres of PGA is found to have an adequate mechanical consistency and rigidity even though it is a flexible and biodegradable textile. In this way the textile can retain its shape and, thanks to its resistance to urine, does not demonstrate any swelling (increase in volume and in dimensions) of the material.

PGA is instead generally used in the art in association with other biopolymers, for example PLA, to form bioabsorbable copolymers which demonstrate lower rigidity and greater flexibility.
The textile of the absorbable patch of the present invention can be made by weaving said yarn or monofilament of PGA in various ways, creating a knit textile, a woven textile or a nonwoven textile. It is preferable to use a warp knit textile in that it has a rougher surface compared to other types.

It is moreover preferable for the textile of the patch to be textured. It has in fact been found that texturing, in addition to making the textile rougher on the surface, also confers greater rigidity and impermeability to urine compared to the non-textured textile. In fact it can be assumed that the texturing goes to cover any micro-holes there may be between the meshes of the textile.

The texturing of the textile can be achieved in various ways: through the use of a rough surface monofilament obtained according to the methods known in the art; via a heat-setting treatment of the textile to obtain raised parts in the fibres, conferring greater volume to the filament. The latter method of texturing is preferred.

Further features of the invention will be made clearer by the following detailed description, referred to its embodiments purely by way of a non-limiting example and illustrated in the accompanying drawings, wherein:

Fig. 1a is a plan view from above of a non-textured patch according to a first embodiment of the invention;
Fig. 1b is a plan view from below of the patch of Fig. 1a;
Fig. 2 is an enlarged view in transverse section of a portion of the patch, wherein the section has been taken along plane II-II of Fig. 1;
Fig. 3 is a plan view of a patch according to the invention comprising a hole for the passage of a ureter, shown at the side intended to be turned towards the exterior of the bladder;
Fig. 4 is a perspective view, illustrating schematically the application to a bladder of the patch according to the invention;
Fig. 5a is a plan view from above of a textured and reinforced patch;
Fig. 5b is a plan view from below of the patch of Fig. 5a;
Fig. 6 is an enlarged view in transverse section of a portion of patch, wherein the section has been taken along plane VI-VI of Fig. 5a,

Referring to Figs. 1 - 2, a patch according to a first embodiment of the invention is described, denoted by reference numeral 1.
The term "patch" here refers to substrates different from those known as "mesh", "mesh tape" or reinforcement nets normally used in combination with sheets or membranes of bioabsorbable materials. Contrarily the present patch, thanks to its mechanical consistency, can be used alone without the need for support thanks to the fact of being a spun textile.

In Figs. 1a-1b the patch 1 is shown with a rectangular shape, even if this shape is not binding for the purposes of the present invention. The patch 1 is made up of a textile 2 (Fig. 2) obtained from an ultra-lightweight monofilament of PGA bioabsorbable polymer.

This textile 2 preferably has a denier count (also known as "linear mass density") or grams per square metre comprised between 240 and 320 deniers, The term "denier", "D", indicates the weight of the textile, where 1D corresponds to 9,000 metres of yarn with weight 9,000 g (P(g) / L(9,000 m)).

This textile 2 is made from monofilament of PGA having a denier count preferably comprised between 120 and 160 deniers, where the deniers here refer to the diameter of the monofilament.

The thickness of this textile 2 is fairly small and such as to result in a sufficiently elastic patch 1 for being able to withstand the dilations due to the expansion and to the subsiding of the bladder.

Said patch 1 has moreover the upper surface 3 substantially equal to the lower surface 4, smooth and non-textured. Upper surface refers to the surface turned towards the exterior of the bladder intended to come into contact with the internal tissues of the patient while lower surface refers to that turned towards the interior of said bladder.

The surface 3 guarantees non-fusion with the internal tissues of the patient with which it comes into contact since it is made of PGA, even if it is preferable to perform the texturing to increase further the non-adherence of the patch to the fibrotic capsule.

Referring to Figs. 3-4 a description is given of a patch 100 according to a second embodiment of the invention, wherein identical elements or elements corresponding to those already described are denoted by the same reference numerals and their detailed description is omitted.

In this case the patch 100 provides for the textile 2 of PGA to have a hole 5 having a
diameter greater respectively than the diameter of the ureters 20, 20' and of the urethra 21 (shown in Fig. 4). This hole 5 can have a diameter of 20 mm.

The hole 5 is preferably formed during the operation and is made with a special surgical instrument consisting of a handpiece or punch, in accordance with the possible dimensions of the ureters 20, 20' or of the urethra 21.

Referring to Figs. 5a, 5b and 6 a description is given of a textured and reinforced patch according to the invention, denoted overall with reference numeral 200.

Said patch 200 is represented with a rectangular shape, even if this shape is not binding for the purposes of the invention. The patch 200 is also made up of a textile 2 made from a yarn of PGA fibres, which can also be monofilament.

Said textile 2 is warp knitted and the structure thereof is such that the interstitial space is smaller than 100 microns. This guarantees impermeability to urine, avoiding leaks.

The textile 2 of the patch 200 is made with yarns having dimensions of around 50-200 deniers, monofilament or multifilament.

The yarn of the textile 2 of the patch 200 is preferably 75 deniers/30 filaments (parallel one to the other) and is textured.

The warp knitting process does not allow the obtaining of a woven or nonwoven material or a felt-like material.

This process of warp knitting is carried out preferably with a work pattern of the type

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<td>courses per inch (CPI)</td>
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With this work pattern and with the prefed yarn indicated above a textile 2 is obtained with the following features:

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<td>surface density, mg/em²</td>
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The thickness of this textile 2 is substantially similar to what is indicated in the previous embodiments. The thickness of the textile 2 is preferably around 0.53 mm.

The upper 3 and lower 4 surfaces appear very rough since the textile 2 has been subjected to texturing, in addition to the warp knit process.

Moreover the lower surface 4 has four reinforcement strips 30 made with the same textured textile 2 described above, preferably having the same thickness as the textile 2. They can be attached as a cross, star or parallel one to the other, even if this is not binding for the purposes the invention. Moreover the number of the reinforcement strips can be higher or lower than four without departing from the scope of the invention. The number of strips and their positioning on the surface 4 depend essentially on the size of the patch and therefore on the portion of bladder to be replaced.

Said strips 30 are made to adhere to the surface 4 by ultrasound welding, thus avoiding the use of adhesive materials which could give rise to undesirable reactions.

In the ultrasonic technology the vibrations produced create the heat necessary for melting the materials in the point of joining. The parts which have to be welded are held together under pressure and subjected to ultrasonic vibrations by means of the sonotrode which transmits energy in the form of vibrations directly to the parts which have to be assembled, also applying thereto a welding pressure. The PGA of the textile 2 fuses with the PGA of the strips 30 and the two materials weld when cooling starts.

The patch 200 can be provided with a hole 5 (not illustrated in Figures 5a, 5b, 6), as described above, having a diameter greater than the diameter of the ureters 20, 20' and of the urethra 21 (shown in Fig. 4) respectively. This hole 5 generally has a diameter of 20 mm.

Alternatively said hole 5 can preferably be made in the patch 200 during the operation using a special surgical instrument consisting of a handpiece or punch, in accordance with the possible dimensions of the ureters 20, 20' or of the urethra 21.

As mentioned the patches 1, 100 and 200 can be made in any shape and size. The patches 1 and 100 preferably have a rectangular 200 mm x 300 mm, 100 mm x 200 mm or square
shape with a side of 200 mm.

The thickness of the patch is also not binding for the purposes of the present invention: in one embodiment said thickness is approximately 0.53 mm.

Preparation of the patch of the invention takes place in a controlled environment or with controlled contamination, in a clean room. Once processing has finished, the patch is placed in a double blister closed with a sheet of Tyvek to avoid contaminations, and sent to a cycle of sterilisation with a base of EtO (ethylene oxide). At this point the patch is ready for use in an operation.

The choice of the dimensions of the monofilament of PGA which makes up the textile of the patch 1,100 and 200, of the dimensions, the thicknesses and the denier count of said patch is made essentially as a function of the age of the patient and/or of his or her metabolism. Therefore the features mentioned above must be such as to avoid, during the process of absorption, inflammatory phenomena or situations caused by absorption in inappropriate times, i.e. too fast in relation to the metabolism of the patient.

The Applicant has surprisingly found that the patches made in PGA as described above, more particularly those textured and/or reinforced, demonstrate a good mechanical consistency and adequate rigidity, also in the presence of urine, so that they are able to guarantee correct deformation of the bladder during emptying or filling of the same, demonstrating at the same time good tightness against leaks of urine.

In fact the patches of the present invention possess a combination of properties which cannot be found in other known patches:
- adequate rigidity such as to allow the bladder to retain its shape until absorption of the patch and not to collapse under the weight of the growing tissues;
- adequate elasticity and flexibility such as to ensure the correct deformation of the patch during the natural functioning of the bladder whereon the patch is applied;
- chemical resistance and impermeability to urine;
- non-collapsibility;
- non-adherence to the fibrotic capsule.

In fact tests performed by the Applicant using identical textiles yet made with a different bioabsorbable polymer such as PLA have shown that the latter polymer, widely used in
the medical sector, cannot be used advantageously as a patch for the replacement of portions of bladder.

More particularly preclinical studies have been carried out \textit{in vivo} on a pig bladder implanted with a square patch (8-10 x 8-10 cm) in PLA (polylactic acid), monofilament, non-textured and having a denier count between 120 and 160 deniers, in order to assess the behaviour of the patch as a replacement of a portion of bladder in the period of absorption (two months) by the analysis of the cicatrisation, of the integration of the patch in the tissues, of the kidney function and of the lack of local systemic effects. The animal was kept under control by means of ultrasound examination and laboratoiy analysis, starting from the day of the operation, of the blood for up to two months (time of absorption of the PLA).

After 14 days it was observed through the ultrasound examination that the patch had attached to the walls of the bladder and that the site of the implant showed a remodelling with thickening of the bladder wall in its proximity.

The examination two months after implanting demonstrated adherences of the intestine and of the womb to the area of the bladder whereon the patch was implanted and the presence of dark colour zones in the scar of the implant zone, an indicator of remodelling of the zone,

Moreover the histological examination of this implant zone showed that the scar was formed by mature granulation tissue and incorporated the remaining patch.

These phenomena indicate that the portion of bladder removed was not replaced by a new wall of cell tissue of the same dimensions and that the patch must have collapsed onto itself given that it was integrated in the scar tissue. Moreover the composition of the new wall, i.e. of the scar tissue, was demonstrated to be mainly mature granulation tissue not covered by urothelium.

Therefore the patch in PLA has been demonstrated to have a lesser mechanical consistency and a longer absorption time compared to the time of regeneration of the cells of the bladder, influencing the growth of the new biological wall tissue of the portion of bladder removed and the growth of the urothelium: this meant that the growing tissue did not replace that being absorbed, therefore growing in other directions. The
result is a bladder which tends to have an asymmetrical and abnormal shape, different from the original one, so that it is potentially irksome to the other surrounding organs.

Moreover the patch in PLA has been shown to have a poor mechanical consistency and rigidity in the presence of urine and was found to be too soft.

Fig. 4 illustrates schematically a bladder 40 with the relative ureters 20, 20' and urethra 21.

If the zone of the bladder 40 affected by neoplasia is distant from the ureters 20, 20' and urethra 21, the surgeon removes this affected zone and, in order to cover the removal hole, applies a patch 1 by means of stitches 7 which connect the perimeter of the patch 1 to the wall of the bladder 40 around the removal hole.

Fig. 4 also illustrates the case wherein the zone of the bladder 40 affected by neoplasia is close to one of the ureters 20, 20'. In this case the surgeon removes this affected area, detaching it from the relative ureter 20. Then the surgeon forms a hole 9 in the patch 1 (corresponding to the hole 5 described previously) using a handpiece or punch similar to that used to perforate the textile 2 of the patch 100, whose tip is chosen on the basis of the dimensions of the ureter 20. The hole 9 is then formed with the measurement, in Ch, which the surgeon considers appropriate on the basis of the dimensions of the ureter 20 in the operation.

The ureter 20 is inserted in the hole 9 of the patch 100 which, being elastic, tightens slightly around the tube of the ureter 20. Then the ureter 20 is attached to the patch 1 by means of four stitches 11 arranged in a square, around the tube of the ureter 20 and passing through the patch 1 and through the tissue of the ureter 20.

Finally the perimeter of the patch 100 is attached, by means of stitches 10, to the wall of the bladder 40 around the ureter 20.

The stitches 7, 10 and 11 are formed with a curved cylindrical needle using a monofilament yam in bioabsorbable (absorbable) material like that that deriving from polymers or copolymers of PGA. The motivation behind this choice lies in the need for the patch and stitches to be absorbed in the same space of time.
There are however other suture yarns in bioabsorbable polymers which could conveniently suit the cases in question and the needs of the patches according to the decision of the surgeon.

The holes of passage of the stitches 7, 11 and 10 in the ureter 20 and in the bladder 40 do not constitute a risk of leaks of liquid, in that in a few hours the tissue is reconstructed. To avoid leaks of urine (liquid) the holes of the stitches 7, 11 and 10 are welded and closed with one cc. (a drop) of surgical glue, such as for example Glubran 2™, normally available commercially.

When the neoplasia is close to one of the ureters 20, 20' it is also possible to use the patch 1 as an alternative to the patch 100. In this case the hole 9 is formed directly in the textile 2 instead of in the membrane 6 using the same handpiece or punch described above.

The same procedure described hitherto can also be applied to a textured and reinforced patch 200.

One of the advantages of the patches of the present invention is that they do not have any risk of adherence of the fibrotic capsule to the patch in that they are fully absorbable during the regeneration of the area removed and therefore do not require their removal from the organ wherein they were implanted by subsequent procedures. The time of complete absorption may vary from 6 months to about 1 year according to the metabolism of the patient and the features of the patch indicated previously.

The use of the patches of the present invention is particularly advantageous in the treatment of localised infections of the bladder such as bilharzia where the removal of the infected part of the bladder is adequate for ensuring recovery from the disease, without the need for subsequent treatments or procedures.

Numerous detail modifications and changes may be made to the present embodiments of the invention, within the reach of the person skilled in the art and in any case coming within the sphere of the invention expressed by the annexed claims,
1. A bioabsorbable patch (200) of polyglycolic acid (PGA) for the replacement of a portion of bladder (40) wall, following partial cystectomy, characterised in that it is formed by a textured textile (2) made of yarns of fibres of said PGA and in that it is provided with one or more reinforcement strips (30) made up of the same textured textile (2), positioned on the lower surface (4) of said patch to be turned towards the interior of said bladder (40),

2. Patch (200) according to claim 1, wherein the yarn, monofilament or multifilament, has a dimension comprised between 50 and 200 deniers.

3. Patch (200) according to claim 1 or 2, wherein the textile (2) is a warp knit textile.

4. Patch (200) according to any one of the previous claims, wherein the yarn of the textile (2) is 75 deniers/30 filaments.

5. Patch (200) according to any one of the previous claims, wherein said strips (30) are applied as to form a cross, star or parallel one to the other,

6. Patch (200) according to any one of the previous claims, wherein said strips (30) are applied by ultrasound welding.

7. Patch (200) according to any one of the previous claims, wherein said strips (30) are four and are applied as to form a cross.

8. Patch (200) according to any one of the previous claims, wherein its shape is rectangular with dimensions 200 mm x 300 mm, 100 mm x 200 mm, or square with a side of 200 mm.

9. Patch (200) according to any one of the previous claims, characterised in that it comprises a hole (5) with a diameter greater than the diameter of the ureters (20, 20') and of the urethra (21).

10. Patch (200) according to any one of the previous claims, characterised in that it has a thickness of about 0.53 mm.
**INTERNATIONAL SEARCH REPORT**

International application No
PCT/EP2010/067375

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61F2/04
ADD.

According to International Patent Classification (IPC) and/or both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Relevant to claim No.</th>
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<td>US 2003/120352 A1 (ATALA ANTHONY [US]) 26 June 2003 (2003-06-26) paragraphs [0001], [0009], [0010], [0014], [0015], [0021], [0022] paragraph [0025] - paragraph [0027] example 2</td>
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<td>A</td>
<td>EP 1 060 714 A2 (ETHICON INC [US]) 20 December 2000 (2000-12-20) paragraphs [0013], [0 15], [0 19], [0 21] claims 5, 8</td>
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X Further documents are listed in the continuation of Box C. X See patent family annex.

- Special categories of cited documents:
  - A * document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search: 12 January 2011

Date of mailing of the international search report: 20/01/2011

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European Patent Office, P.B. 5818 Patentlaan 2
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Fax (+31-70) 340-3016

Authorized officer
Mary, Celine

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<td>A</td>
<td>US 4 655 221 A (DEVEREUX DENNIS F [US]) 7 April 1987 (1987-04-07) column 4, line 8 - line 20 column 6, line 1 - column 8, line 13</td>
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<td>A</td>
<td>FR 2 255 877 A1 (RHONE POULENC IND [FR]) 25 July 1975 (1975-07-25) figures 1,2 page 4, line 18 - line 20</td>
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