Modified AAV Capsid Proteins for Treatment of Arthritic Disease

Field of the invention

The invention relates to the field of recombinant adeno-associated virus (rAAV) based gene therapy, in particular to the use of a mutant capsid rAAV in the treatment or prevention of an arthritic disease.

Background of the invention

Recombinant adeno-associated virus (rAAV) vectors have demonstrated excellent safety and efficacy profiles for the delivery of genes in humans *in vivo*. Therefore, rAAV vectors have been extensively used for *in vivo* gene therapy and have been shown safe and effective in pre-clinical models as well as in clinical trials. rAAV vectors have been successful in a number of gene therapy clinical trials for a range of diseases including haemophilia B, haemophilia A, cystic fibrosis, alpha-1 anti-trypsin deficiency, spinal muscular atrophy (SMA), Parkinson disease, Duchenne muscular dystrophy and Leber's congenital amaurosis (Selot *et al.*, Current Pharmaceutical Biotechnology, 2013, 14, 1072-1082). Alipogene tiparvovec (Glybera®, uniQure) has been granted marketing authorization in Europe as a gene therapy for the treatment of lipoprotein lipase deficiency (LPLD). Subsequently, gene therapy drug approval was granted for herpes-virus based Talimogene laherparepvec for the treatment of skin cancer (T-Vec, Imlygic®, Amgen) and for *ex vivo* stem cell retroviral-based gene therapy Strimvelis for the treatment of ADA-SCID (GSK).

rAAV vector-based gene therapy has also been applied in rheumatoid arthritis (RA), which is a chronic inflammatory disease that affects ~1% of the population. The pathology of RA extends throughout the synovial joint. The localized nature of the joint makes *in vivo* gene therapy very attractive. Therapies providing anti-inflammatory proteins aimed at shifting the balance in RA towards an anti-inflammatory state have been applied.

Much work has focused on the development of AAV capsid proteins with desired properties. Such properties can include higher transduction efficiency, tissue/organ tropism, de-targeting of non-desired tissues/organs, or avoidance of pre-existing neutralizing antibodies.

There is, however, still a need in the art to further improve rAAV gene therapy vectors. In particular, there is a need to improve the use of rAAV gene therapy vectors in arthritic disease and, more precisely, to improve the efficiency of delivering genetic material to the targeted tissue, such as the synovial joint or specific cell types within the synovial joint, preferably to fibroblast-like synoviocytes (FLS).

Summary ~~of the invention~~

In one aspect, the present disclosure relates to a use of recombinant adeno-associated virus (rAAV) virion comprising a modified capsid protein and a promoter operably linked to a nucleotide sequence encoding a gene product of interest in the manufacture of a medicament for treating or preventing an arthritic disease or for treating or preventing symptoms associated

with an arthritic disease, wherein the gene product of interest is an IL-6 inhibitor; and the modified capsid protein comprises in the C-terminal part of the protein an amino acid sequence Z, residues of which are exposed on the surface of the capsid protein, wherein the amino acid sequence Z:

a. comprises or consists of a sequence of amino acid residues of the formula I:

$$y – G – Q – x – G – (x)_3 – R – (x)_3 – y – A – Q – A – A$$

wherein x represents a single amino acid residue and wherein y represents 0, 1 or 2 amino acid residues; and

b. is present at a location corresponding to a position 100 – 200 amino acid residues from the C terminus of a wild-type AAV capsid protein.

In another aspect, the present disclosure relates to a use of an rAAV composition in the manufacture of a medicament for treating or preventing an arthritic disease or for treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition comprises an rAAV virion as defined herein and a pharmaceutically acceptable carrier.

In yet another aspect, the present disclosure relates to a use of an rAAV composition and an immunosuppressant in the manufacture of a combination therapy for treating or preventing an arthritic disease or for treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition is as defined herein.

In some ~~aspect~~examples, the ~~invention~~disclosure relates to the following numbered ~~embodiment~~examples:

~~Embodiment~~Example 1. A recombinant adeno-associated virus (rAAV) virion comprising a modified capsid protein and a promoter operably linked to a nucleotide sequence encoding a gene product of

interest, wherein the rAAV virion is for use in treating or preventing an arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein the modified capsid protein comprises in the C-terminal part of the protein an amino acid sequence Z, residues of which are exposed on the surface of the capsid protein, preferably wherein the product of interest is an immunosuppressant.

~~Embodiment~~Example 2. An rAAV virion for use according to ~~embodiment~~example 1, wherein the amino acid sequence Z:

a. comprises or consists of a sequence of amino acid residues of the formula I:

$$y - G - Q - x - G - (x)_3 - R - (x)_3 - y - A - Q - A - A$$

wherein x represents a single amino acid residue and wherein y represents 0, 1 or 2 amino acid residues; and

b. is present at a location corresponding to a position 100 – 200, preferably 120 – 180, more preferably 130 – 170, more preferably 140 – 160 amino acid residues from the C terminus of a wild-type AAV capsid protein.

~~Embodiment~~Example 3.An rAAV virion for use according to ~~embodiment~~example 1 or 2, wherein the gene product of interest is an IL-6 inhibitor.

~~Embodiment~~Example 4.An rAAV virion for use according to ~~embodiment~~example 1 or 2, wherein the gene product of interest is an TNFα inhibitor.

~~Embodiment~~Example 5.An rAAV virion for use according to ~~embodiment~~example 1 or 2, wherein the gene product of interest is an IL-1 inhibitor.

~~Embodiment~~Example 6.An rAAV virion for use according to ~~embodiment~~example 3, wherein the IL-6 inhibitor is selected from the group consisting of an IL-6 receptor antagonist, a humanised anti-IL-6 monoclonal antibody, a chimeric anti-IL-6 monoclonal antibody, a humanized rabbit anti-IL-6 monoclonal antibody and a soluble IL-6 receptor, preferably wherein at least one of

i) the IL-6 receptor antagonist is at least one of tocilizumab and sarilumab;

ii) the humanised anti-IL-6 monoclonal antibody is at least one of olokizumab and sirukumab;

iii) the chimeric anti-IL-6 monoclonal antibody is siltucimab; and

iv) the humanized rabbit anti-IL-6 monoclonal antibody is clazakizumab.

~~Embodiment~~Example 7. An rAAV virion for use according to ~~embodiment~~example 4, wherein the TNFα inhibitor is selected from the group consisting of etanercept, infliximab, adalimumab, certilizumab pegol and golimumab, preferably wherein the TNFα inhibitor is etanercept.

~~Embodiment~~Example 8. An rAAV virion for use according to ~~embodiment~~example 5, wherein the IL-1 inhibitor is selected from the group consisting of

i) an IL-1 receptor antagonist, preferably a human IL-1 receptor antagonist, preferably the human IL-1 receptor antagonist anakinra;

ii) an anti-IL-1 monoclonal antibody, preferably a human anti-IL-1 monoclonal antibody, preferably the human IL-1 monoclonal antibody canakinumab or gevokizumab

iii) a human dimeric anti-IL-1 fusion protein, preferably the human dimeric anti-IL-1 fusion protein rilonacept; and

iv) a human dual variable domain anti-IL-1 immunoglobulin, preferably the human dual variable domain anti-IL-1 immunoglobulin lutikizumab.

~~Embodiment~~Example 9.An rAAV virion for use according to any one of the preceding ~~embodiment~~examples, wherein the promoter is a constitutive promoter or an inducible promoter, preferably the promoter is an NFκB responsive promoter, preferably an NFκB responsive CMV promoter, preferably an NFκB responsive minimal CMV promoter.

~~Embodiment~~Example 10. An rAAV virion for use according to any one of the preceding ~~embodiment~~examples, wherein the sequence Z is comprised in the modified capsid protein at a location represented by the formula II:

$$EEEIxxxxPVATExxGxxxxNxQy - Z - (x)_nLPGMVWQxRDVYLQGPIWAKIPHTDG$$

a. wherein Z, x and y are as defined in ~~embodiment~~example 2; and
b. wherein n is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

~~Embodiment~~Example 11. An rAAV virion for use according to any one of the preceding ~~embodiment~~examples, wherein the capsid protein comprises an amino acid sequence selected from the group consisting of:

i) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 1 and wherein amino acids at positions 588 – 602 of SEQ ID NO: 1 have at least 80% sequence identity with SEQ ID NO: 11,

ii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 2 and wherein amino acids at positions 585 – 602 of SEQ ID NO: 2 have at least 80% sequence identity with SEQ ID NO: 10,

iii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 3 and wherein amino acids at positions 587 – 601 of SEQ ID NO: 3 have at least 80% sequence identity with SEQ ID NO: 9,

iv) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 4 and wherein amino acids at positions 586 – 600 of SEQ ID NO: 4 have at least 80% sequence identity with SEQ ID NO: 8,

v) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 5 and wherein amino acids at positions 588 - 602 of SEQ ID NO: 5 have at least 80% sequence identity with SEQ ID NO: 9,

vi) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 6 and wherein amino acids at positions 588 - 602 of SEQ ID NO: 6 have at least 80% sequence identity with SEQ ID NO: 8, and

vii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 7 and wherein amino acids at positions 587 – 604 of SEQ ID NO: 7 have at least 80% sequence identity with SEQ ID NO: 12,

wherein the modified capsid protein provides for an at least two-fold increase in expression, preferably in human FLS cells, in comparison to an unmodified capsid protein with an amino acid sequence selected from the group consisting of SEQ ID NO: 13 – 19, when tested under the same conditions, wherein preferably the unmodified capsid protein has the amino acid sequence SEQ ID NO: 19 or has the same serotype as the modified capsid protein.

~~Embodiment~~Example 12. An rAAV virion for use according to any one of the preceding ~~embodiment~~examples, wherein the capsid protein comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NO:1 – 7, preferably wherein the capsid protein comprises or consists of SEQ ID NO: 4 or SEQ ID NO: 6.

~~Embodiment~~Example 13. An rAAV composition for use in treating or preventing an arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition comprises an rAAV virion as defined in any one of ~~embodiment~~examples 1 - 12 and a pharmaceutically acceptable carrier.

~~Embodiment~~Example 14. An rAAV composition and an immunosuppressant for use in treating or preventing an arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition is as defined in ~~embodiment~~example 13 and wherein the treatment or prevention comprises the administration of the rAAV composition and the administration of the immunosuppressant to an individual.

~~Embodiment~~Example 15. An rAAV virion for use according to any one of ~~embodiment~~examples 1 – 12, an rAAV composition for use according to ~~embodiment~~example 13, or an rAAV composition and an immunosuppressant for use according to ~~embodiment~~example 14, wherein the arthritic disease is selected from the group consisting of rheumatoid arthritis (RA), juvenile rheumatoid arthritis, osteoarthritis (OA), gout, pseudogout, spondyloarthritis (SpA), psoriatic arthritis, ankylosing spondylitis, septic arthritis, arthritis, juvenile idiopathic arthritis, blunt trauma, joint replacement and Still's disease.

~~Embodiment~~Example 16. An rAAV virion for use according to any one of ~~embodiment~~example 1 - 12 or an rAAV composition for use according to ~~embodiment~~example 13, wherein the rAAV virion and/or the rAAV composition is administered systemically and/or locally.

~~Embodiment~~Example 17. An rAAV composition and an immunosuppressant for use according to ~~embodiment~~example 14, wherein at least one of the rAAV composition and the immunosuppressant is administered locally.

~~Embodiment~~Example 18. An rAAV virion or an rAAV composition for use according to ~~embodiment~~example 16 and/or an rAAV composition and an immunosuppressant for use according to ~~embodiment~~example 17, wherein the local administration is intraarticular administration.

Detailed description of the invention

The inventors have discovered that a recombinant adeno-associated virus (rAAV) virion comprising a modified capsid protein is surprisingly efficient at transducing cells, and in particular efficient at transducing cells of the synovial joint.

Primary target cells in the joint in the treatment of arthritic diseases, such as for example rheumatoid arthritis include, but are not limited to, fibroblast-like synoviocytes (FLS), cartilage cells, chondrocytes and chondroblasts. The aim of the present invention is to provide for capsid proteins which are improved in one or more of the following properties: i) higher expression levels in the joint tissue, in particular in FLS; ii) improved joint tissue tropism, in particular improved tropism for FLS; and/or iii) improved de-targeting from non-desired tissues/organs upon rAAV administration as compared to capsid proteins known in the art. In particular, these properties of the rAAV virion comprising a modified capsid protein of the invention are improved as compared to unmodified capsid proteins, preferably the wild-type capsid protein of the same serotype as the modified capsid protein and/or AAV5 capsid proteins. It has been previously established that AAV5 capsid gives rise to the highest FLS expression levels when compared with other AAV serotypes (Adriaansen et al. (2005) Ann Rheum Dis 64:1677-1684; Apparailly et al. (2005) Hum. Gene Ther. 16:426-434). As it is the capsid that confers the tissue/cell tropism properties, the modified capsids described in this invention have the property of enhanced FLS transduction potential preferably when compared with unmodified AAV5. In particular, it is preferred that the capsid proteins of the present invention provide higher expression levels in synovial tissue, in particular in FLS, preferably upon intraarticular administration, as compared to unmodified capsid proteins (that is, the same capsid protein without the modification that is to be tested, preferably of the same serotype as the modified capsid proteins), preferably wild-type unmodified capsid proteins (preferably of the same serotype as the modified capsid proteins), more preferably unmodified AAV5 or wtAAV5 capsid proteins.

Hence, in a first aspect, the invention pertains to an rAAV virion comprising a modified capsid

Claims

1. Use of~~A~~ recombinant adeno-associated virus (rAAV) virion comprising a modified capsid protein and a promoter operably linked to a nucleotide sequence encoding a gene product of interest in the manufacture of a medicament for treating or preventing an arthritic disease or for treating or preventing symptoms associated with an arthritic disease, wherein the gene product of interest is an IL-6 inhibitor; and~~rAAV virion is for use in treating or preventing an arthritic disease or for use in treating or preventing symptoms associated with an arthritic disease, wherein~~ the modified capsid protein comprises in the C-terminal part of the protein an amino acid sequence Z, residues of which are exposed on the surface of the capsid protein, ~~preferably wherein the product of interest is an immunosuppressant.~~

~~2. An rAAV virion for use according to claim 1,~~ wherein the amino acid sequence Z:

a. comprises or consists of a sequence of amino acid residues of the formula I:

$$y – G – Q – x – G – (x)_3 – R – (x)_3 – y – A – Q – A – A$$

wherein x represents a single amino acid residue and wherein y represents 0, 1 or 2 amino acid residues; and

b. is present at a location corresponding to a position 100 – 200~~, preferably 120 – 180, more preferably 130 – 170, more preferably 140 – 160~~ amino acid residues from the C terminus of a wild-type AAV capsid protein.

2. The use according to claim 1, wherein the amino acid sequence Z is present at a location corresponding to a position 120 – 180 amino acid residues from the C terminus of a wild-type AAV capsid protein.

3. The use according to claim 2, wherein the amino acid sequence Z is present at a location corresponding to a position 130 – 170 amino acid residues from the C terminus of a wild-type AAV capsid protein.

4. The use according to claim 3, wherein the amino acid sequence Z is present at a location corresponding to a position 140 – 160 amino acid residues from the C terminus of a wild-type AAV capsid protein.

~~3. An rAAV virion for use according to claim 1 or 2, wherein the gene product of interest is an IL-6 inhibitor.~~

~~4. An rAAV virion for use according to claim 1 or 2, wherein the gene product of interest is an TNFα inhibitor.~~

~~5. An rAAV virion for use according to claim 1 or 2, wherein the gene product of interest is an IL-1 inhibitor.~~

~~6~~5. ~~An rAAV virion for~~The use according to claim ~~3~~1, wherein the IL-6 inhibitor is selected from the group consisting of an IL-6 receptor antagonist, a humanised anti-IL-6 monoclonal antibody, a chimeric anti-IL-6 monoclonal antibody, a humanized rabbit anti-IL-6 monoclonal antibody and a soluble IL-6 receptor.

6. The use according to claim 1, ~~preferably~~ wherein at least one of:

i) the IL-6 receptor antagonist is at least one of tocilizumab and sarilumab;

ii) the humanised anti-IL-6 monoclonal antibody is at least one of olokizumab and sirukumab;

iii) the chimeric anti-IL-6 monoclonal antibody is siltucimab; and

iv) the humanized rabbit anti-IL-6 monoclonal antibody is clazakizumab.

~~7. An rAAV virion for use according to claim 4, wherein the TNFα inhibitor is selected from the group consisting of etanercept, infliximab, adalimumab, certilizumab pegol and golimumab, preferably wherein the TNFα inhibitor is etanercept~~

~~8. An rAAV virion for use according to claim 5, wherein the IL-1 inhibitor is selected from the group consisting of~~

~~i) an IL-1 receptor antagonist, preferably a human IL-1 receptor antagonist, preferably the human IL-1 receptor antagonist anakinra;~~

~~ii) an anti-IL-1 monoclonal antibody, preferably a human anti-IL-1 monoclonal antibody, preferably the human IL-1 monoclonal antibody canakinumab or gevokizumab~~

~~iii) a human dimeric anti-IL-1 fusion protein, preferably the human dimeric anti-IL-1 fusion protein rilonacept; and~~

~~iv) a human dual variable domain anti-IL-1 immunoglobulin, preferably the human dual variable domain anti-IL-1 immunoglobulin lutikizumab~~

~~97~~. ~~An rAAV virion for~~The use according to any one of the preceding claims, wherein the promoter is a constitutive promoter or an inducible promoter.

8. ~~, preferably~~The use according to claim 7, wherein the promoter is an NFκB responsive promoter.

9. ~~, preferably~~The use according to claim 8, wherein the NFκB responsive promoter is an NFκB responsive CMV promoter.

10. ~~, preferably~~The use according to claim 9, wherein the NFκB responsive CMV promoter is an NFκB responsive minimal CMV promoter~~-~~.

~~10~~11. ~~An rAAV virion for~~The use according to any one of the preceding claims, wherein the sequence Z is comprised in the modified capsid protein at a location represented by the formula II:

EEEIxxxxPVATExxGxxxxNxQy – Z – $(x)_n$LPGMVWQxRDVYLQGPIWAKIPHTDG

a. wherein Z, x and y are as defined in claim ~~2~~1; and
b. wherein n is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15.

~~11~~12. ~~An rAAV virion for~~The use according to any one of ~~the preceding~~ claims 1 to 10, wherein the capsid protein comprises an amino acid sequence selected from the group consisting of:

i) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 1 and wherein amino acids at positions 588 – 602 of SEQ ID NO: 1 have at least 80% sequence identity with SEQ ID NO: 11,

ii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 2 and wherein amino acids at positions 585 – 602 of SEQ ID NO: 2 have at least 80% sequence identity with SEQ ID NO: 10,

iii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 3 and wherein amino acids at positions 587 – 601 of SEQ ID NO: 3 have at least 80% sequence identity with SEQ ID NO: 9,

iv) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 4 and wherein amino acids at positions 586 – 600 of SEQ ID NO: 4 have at least 80% sequence identity with SEQ ID NO: 8,

v) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 5 and wherein amino acids at positions 588 - 602 of SEQ ID NO: 5 have at least 80% sequence identity with SEQ ID NO: 9,

vi) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 6 and wherein amino acids at positions 588 - 602 of SEQ ID NO: 6 have at least 80% sequence identity with SEQ ID NO: 8, and

vii) an amino acid sequence having at least 70% sequence identity with an amino acid sequence having SEQ ID NO: 7 and wherein amino acids at positions 587 – 604 of SEQ ID NO: 7 have at least 80% sequence identity with SEQ ID NO: 12,

wherein the modified capsid protein provides for an at least two-fold increase in expression~~, preferably in human FLS cells,~~ in comparison to an unmodified capsid protein with an amino acid sequence selected from the group consisting of SEQ ID NO: 13 – 19, when tested under the same conditions~~, wherein preferably the unmodified capsid protein has the amino acid sequence SEQ ID NO: 19 or has the same serotype as the modified capsid protein~~.

13. The use according to claim 12, wherein the modified capsid protein provides for an at least two-fold increase in expression in human FLS cells, in comparison to an unmodified capsid protein with an amino acid sequence selected from the group consisting of SEQ ID NO: 13 – 19, when tested under the same conditions.

14. The use according to claim 12 or 13, wherein the unmodified capsid protein has the amino acid sequence SEQ ID NO: 19 or has the same serotype as the modified capsid protein.

~~12~~15. ~~An rAAV virion for~~The use according to any one of ~~the preceding~~ claims 1 to 10, wherein the capsid protein comprises or consists of an amino acid sequence selected from the group consisting of SEQ ID NO:1 – 7.

16. ~~, preferably~~The use according to claim 15, wherein the capsid protein comprises or consists of SEQ ID NO: 4 or SEQ ID NO: 6.

~~13~~17. ~~An~~ Use of an rAAV composition in the manufacture of a medicament for~~for use in~~ treating or preventing an arthritic disease or for ~~use in~~ treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition comprises an rAAV virion as defined in any one of claims 1- ~~12~~ 16 and a pharmaceutically acceptable carrier.

18. The use according to any one of claims 1 to 17, wherein the arthritic disease is selected from the group consisting of rheumatoid arthritis (RA), juvenile rheumatoid arthritis, osteoarthritis (OA), gout, pseudogout, spondyloarthritis (SpA), psoriatic arthritis, ankylosing spondylitis, septic arthritis, arthritis, juvenile idiopathic arthritis, blunt trauma, joint replacement and Still's disease.

~~14~~19. Use of ~~A~~an rAAV composition and an immunosuppressant in the manufacture of a combination therapy for ~~use in~~ treating or preventing an arthritic disease or for ~~use in~~ treating or preventing symptoms associated with an arthritic disease, wherein the rAAV composition is as defined in claim ~~13~~ 17~~and wherein the treatment or prevention comprises the administration of the rAAV composition and the administration of the immunosuppressant to an individual~~.

~~15~~20. ~~An rAAV virion for~~The use according to ~~any one of claims 1 – 12~~claim 19~~, an rAAV composition for use according to claim 13, or an rAAV composition and an immunosuppressant for use according to claim 14~~, wherein the arthritic disease is selected from the group consisting of rheumatoid arthritis (RA), juvenile rheumatoid arthritis, osteoarthritis (OA), gout, pseudogout, spondyloarthritis (SpA), psoriatic arthritis, ankylosing spondylitis, septic arthritis, arthritis, juvenile idiopathic arthritis, blunt trauma, joint replacement and Still's disease.

~~16~~21. ~~An rAAV virion for~~The use according to any one of claims 1 - ~~12~~ 18~~or an rAAV composition for use according to claim 13~~, wherein the rAAV virion ~~and/~~or the rAAV composition is to be administered systemically ~~and/~~or locally.

~~17~~22. ~~An rAAV composition and an immunosuppressant for~~The use according to claim ~~14~~19 or 20, wherein at least one of the rAAV composition and the immunosuppressant is to be administered locally.

~~18~~23. ~~An rAAV virion or an rAAV composition for~~The use according to claim ~~16 and/or an rAAV composition and an immunosuppressant for use according to claim 17~~22, wherein the local administration is intraarticular administration.