



Commentary: Total joint replacement in inhibitor-positive haemophilia: Long-term outcome analysis in fifteen cases

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This commentary review discusses our publication referred above, as invited by the Journal of Immunological Science. Therefore, all data are already published and no new data are provided. The paper deals with 15 surgical cases, performed in 6 patients, which we have reported in the World Journal of Orthopedics.

Haemophilia is a rare inherited X-chromosomally linked bleeding disorder, affecting males. Its prevalence and treatment options vary internationally, associated with the resources of each country. Without replacement therapies of the inherited, deficient coagulation factor (F) VIII (in haemophilia A) and FIX in haemophilia B the disease causes permanent joint damage or other life- and quality-of-life threatening bleeding episodes, due improper haemostasis and wound healing. The prevalence of the two forms of the disease is 1-2:10000 in haemophilia A and 1:30000 in haemophilia B.

The treatment of haemophilia consists of intravenously administered FVIII or FIX as primary prophylaxis in children around the age of one year or after the first bleeds as secondary prophylaxis, but also on demand type of treatment is applied, particularly in countries with less resources or if the bleeding phenotype is mild (in 10-15% of patients). Without advent prophylaxis available, the burden of the disease to the child and family, and later throughout life, is significant, mainly affected by crippling joints, impaired quality of life, including senses of uncertainty and restriction.

Currently, the worst complication of haemophilia is the development of neutralizing antibodies, called inhibitors, against the replacement therapy, mainly targeting FVIII and hampering the management of severe haemophilia A patients. In haemophilia B the inhibitor rate is significantly lower but does occur. This detrimental immunological side effect of inhibitor development is due to the missing gene and exposure to the foreign protein. This usually occurs after the 20-50 first exposure days to the factor concentrate in a frequency of 15-40% of the patients, depending on their gene mutation and immunological, clinical challenges, such as the major bleeds, and viciously, therein the peak treatment moments with FVIII. Sporadic cases may also appear later in life around the age of 60 years via immunological acquired mechanisms, causing acquired haemophilia A (the main deficiency, but other coagulation factor inhibitors may occur). The primary management of inhibitors

is immune tolerance induction (ITI), which consists of high doses of FVIII administration once or twice daily for several months, sometimes even years. If the expensive ITI succeeds, it will clearly reduce morbidity and costs in the future, the payback being highly beneficial. The majority (60-80%) of the patients regain the tolerance to FVIII.

Inhibitor development results in severe spontaneous major bleeding phenotype, which is currently managed with very costly therapies, so-called FVIII bypassing agents (BPA), i.e., activated prothrombin complex concentrates (aPCC) or recombinant active FVII (rFVIIa). Inhibitor patients have a poor quality of life, devastating joint disease and even shortened survival. The orthopaedic treatment options in inhibitor patients using the BPA became possible in high income countries during the past 20 years. The daily securing of the haemostasis with the BPA for 10-14 days and enhanced dosing during the rehabilitation markedly add treatment costs. There are only a few reports on joint arthroplasties in inhibitor-positive haemophilia patients. Generally, the focus is mainly on the immediate haemostatic outcome, and the long-term orthopaedic results are unreported. In our study, from 1991 to 2012, six haemophilia patients with inhibitors (two low; inhibitor titre < or equal to 5 Bethesda units (BU)/ml) and four high responders; inhibitor titre > 5 BU/ml) were operated. The 15 surgical procedures consisted of seven primary TKRs (two bilateral), one uni-condylar knee arthroplasty, one glenohumeral replacement, two ankle arthroplasties, three knee revision arthroplasties and one THR. The mean follow-up for patients with primary knee replacements (8 arthroplasties) was 7.3 years (0.3-20.3; SD 7.6). For the two ankle arthroplasties the follow-up was 6 and 7 years. For the THR and glenohumeral replacement the follow-up was shorter; 2 and 7 months, respectively.

Our study emphasizes long-term and overall outcome of elective life-quality surgery. For example, in our study the surgical outcome was not impaired with occasional early poor/fair haemostasis¹. The main indication for total joint replacement is pain due to destructed target (3 or more bleeds) joint. The range of motion (ROM) is clearly improved, although in severe prolonged joint contractures the soft tissues can limit recovery, even if the components would allow normal ROM. However, in our experience, the quality of life can be improved via diminished pain, even under situations of stationary contractures. Also, the risk for deep infection seemed smaller than reported previously^{2,3}.

Management of inhibitor patients is especially challenging both peri- and postoperatively and due to costs. As the health economic analysis of the topic is lacking, our study provides new data. According to our cost analysis the major cost comprised of the haemostatic replacement therapy (**Table**); in case of high inhibitor-titre, the BPA costs comprised 90 % of the total joint replacement costs, including hospital stay, components, and other medications. The costs were lower in low responding inhibitors and immune-tolerized high responder patients. Thus, the preoperative immune-tolerance induction is the preferred option, due to its cost- and outcome benefits, covering surgery and preventing postoperative bleeds, and especially later complications. The payback time is to be calculated in this specific scenario.

Historically, in the 70's and 80's joint replacements in haemophilia patients had a high infection and even mortality rate, which later turned out to be also due to plasma replacement therapy and HIV infection and AIDS^{4,5}. Unfortunately, many patients were infected because of blood

Table Cost analysis of joint replacements on 6 inhibitor patients for the past decade (since 2005).¹

| Resp | Operation | | Component | TOT eur | HT * eur | HT(%) | Product ® | Hospital stay |
|------|----------------------------|------------|----------------------|---------|----------|--------|----------------|---------------|
| low | knee revision arthroplasty | unilateral | reconstructive | 103200 | 75700 | 73 | Kogenate Bayer | 18 |
| low | knee revision arthroplasty | unilateral | reconstructive | 95400 | 66900 | 70 | Kogenate Bayer | 11 |
| low | ankle arthroplasty | unilateral | primary ankle | 47200 | 35600 | 75 | Kogenate Bayer | 10 |
| low | ankle arthroplasty | unilateral | primary ankle | 60200 | 48800 | 81 | Kogenate Bayer | 12 |
| low | knee hemiarthroplasty | unilateral | unicondylar | 51500 | 41600 | 81 | Amofil | 9 |
| low | knee revision arthroplasty | unilateral | cruciate retaining | 50200 | 36300 | 72 | Amofil | 8 |
| high | knee arthroplasty | bilateral | PS** model + hinge | 350900 | 305500 | 87 | Amofil | 24 |
| | | | | | | | FEIBA | |
| high | hip arthroplasty | unilateral | primary uncemented | 43300 | 27800 | 64 | RefactoAF *** | 8 |
| high | knee arthroplasty | bilateral | reconstructive | 500400 | 445100 | 89 | FEIBA | 24 |
| | | | | | | | NovoSeven | |
| high | knee arthroplasty | unilateral | PS** model | 409900 | 386100 | 94 | FEIBA | 15 |
| | | | | | | | NovoSeven | |
| high | glenohumeral arthroplasty | unilateral | primary glenohumeral | 49800 | 29300 | 59 | RefactoAF *** | 9 |

* HT haemophilia therapy

** PS posterior stabilized

*** successful preoperative ITI, resp = inhibitor responder, low with historical inhibitor titre < 5BU/mL and high with historical inhibitor titre > 6 BU/mL.

products contaminated with, at that time unrecognisable, HIV virus. In Finland, blood products did not transmit HIV, but hepatitis C (HCV) virus, until it was recognised and eliminated with de-lipidation and nanofiltration techniques. Since then, benefits of joint replacements for haemophilia patients are reported, albeit the slight increase in risk for deep infections compared with that of non-haemophilia patients. The surgical data of these rare inhibitor patients are scanty⁶⁻¹². In long-term several confounders occur, i.e. wide variety of prosthesis components, and the lack of unified pre- and postoperative scoring. The total outcome, including bleeding tendency, surgical outcome and quality of life, is, however, crucial for long-term cost effectiveness. The optimal timing for joint replacement in a patient with inhibitors should match with the complete functional ability, including other joint problems and possible soft tissue bleeds. The target joint is usually destructed with severe bone loss and joint contractures, being operatively challenging. As the preventive haemostatic treatment is rapidly progressing, the degree of joint destruction and multiple joint problems will be reduced, and the operative treatment of these patients will approach the treatment of primary joint arthrosis. Hitherto, every effort should focus on avoiding bleeds, which needs firm multidisciplinary teamwork. Therefore, it is essential that these operations are centralized to a professional unit. The coagulation factor replacement should cover prolonged rehabilitation, usually longer than normally in arthrosis.

As said, the therapy of haemophilia is very expensive, especially if inhibitors develop. The typical annual cost would be 0.3-0.8 million euros per patient in Europe. On top of that, the costs of orthopaedic surgery are provided in the Table.

This challenging disease has stimulated recent developments to bypass the single missing coagulation factor and produce thrombin, the key enzyme in the coagulation cascade. These approaches include a bispecific antibody, mimicking the function of FVIII, emicizumab, allowing haemostasis to improve, and leading to major (80-90%) reduction in the frequency of bleeding events. The once weekly subcutaneous instead of twice or thrice weekly intravenous drug administration is convenient. The other two novel subcutaneous regimens downplay the naturally occurring anticoagulant mechanisms, tissue factor pathway inhibitor (concizumab) and antithrombin (fitusiran). This treatment progress will be a major paradigm shift, if considered safe and health economical. Also, for haemophilia B successful gene therapy is becoming

a reality¹³, as around 100 patients have been nearly cured from their severe disease. The future of haemophilia appears bright, but we need to pay attention to the safety and monitoring issues of these new therapies¹⁴. Meanwhile still worldwide many patients face with significant problems, lack of care and major inability in daily life due to their poor joint health and muscle condition – a lot to improve and gain.

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