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Perioperative Management of Immunosuppression in rheumatic diseases – What to do?

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Abstract

To stop or not to stop immunosuppressive therapy in the perioperative setting puts the clinician to a challenge. The risk of potential wound infection with possible septic or even lethal consequences needs to be weight against exacerbation of the rheumatic disease. However, exacerbation of autoimmune inflammatory activity needs to be treated with increasing immunosuppressive medication, thus leading to enhanced risk of local and systemic infection as well.

Unfortunately, up to now there is no data from randomized, double-blind controlled clinical trials available on how to steer immunosuppressive therapy in the perioperative setting, making evidence-based recommendations difficult. Neither is there good evidence, if the risk of infectious complications under immunosuppressive therapy differs according to the type and localization of surgery performed. Finally, immunosuppressive co-medication, like glucocorticoid dosage, is not adequately addressed in the available studies, making interpretation of these studies even more problematic. Therefore, a decision has to be made on an individual basis. We discuss the available data on DMARD and biologics therapy in the perioperative setting and describe our own perioperative management with different DMARDs and biologics.

Introduction

In chronic inflammatory diseases, drugs with varying potency to modulate immune functions are utilized. The therapeutic effect may range from mild to intense immusuppression mediated by drugs that can influence specifically or non-specifically certain immune mechanisms. In addition, it is of importance if immunosuppressive mono therapy or combination therapy is instituted. Inhibiting multiple immune mechanisms may more likely lead to a more intense immunosuppression compared to targeting few. It has been demonstrated that certain combinations of immunosuppressive drugs like anti-IL-1 receptor antagonist and anti-TNF-treatment in patients with rheumatoid arthritis resulted in an unacceptably high rate of infections and neutropenia [1]. Thus, this combination is not recommended.

Susceptibility to infection is also determined by the targeted immune mechanisms because different infectious pathogens are attacked by the immune system through specific dominating immune mechanisms. As an example, this was shown in patients following T-cell depleting therapies with occurrence of enhanced rates of viral and fungal infections [2]. Finally, the degree of immunosuppression depends on the given dosage [3].

However, not only pharmacological and pharmacodynamical considerations are important with respect to enhanced susceptibility to infections. Chronic inflammatory processes themselves seem to make the organism more susceptible. Patients with chronic arthritis seem to be at an enhanced risk for infectious arthritis [4]. This enhanced risk of infections may dependent on the severity [4] of the underlying disease and is estimated up to 10-fold in the literature [5].
Discussing immunosuppressive therapy in the context of surgery, one also needs to look at the effects of these drugs on wound healing, for example under glucocorticoids. These drugs are frequently used perioperatively, confering strong inhibitory effects on cell proliferation which may compromise wound healing [6,7]. Compromised and retarded wound healing may give pathogens a greater chance to cause infection.

In contrast to the enhanced risk of wound infection and compromised wound healing during immunosuppressive therapy, there may be an enhanced risk of exacerbation of the underlying inflammatory disease during reduced or paused immunosuppressive therapy. If clinical worsening and rising inflammatory markers during phases of reduced immunosuppressive therapy occur, the physician faces the difficult question whether the situation is caused by infection or exacerbation of the underlying disease. A decision on how to adapt therapy in this perioperative situation needs to be made. Retarding antibiotic therapy and continued immunosuppressive therapy may put the patient at enhanced risk of sepsis and its consequences, and reducing immunosuppressive therapy may put the patient into severe inflammatory bout of the underlying auto-inflammatory disease. However, if inflammatory exacerbation takes place there is the need to enhance immunosuppressive therapy, usually initiated with a pulse of glucocorticoids. Enhancing immunosuppressive therapy in the perioperative setting with fresh wound sites and reduced mobility of the patient may lead to enhanced risk of local and systemic infectious complications like pneumonia and in the worst case septic complications. Another aspect of reducing immunosuppressive therapy prior to surgery may be problem of disease exacerbation by itself. A patient with enhanced inflammatory activity of joints in the post-operative setting might not be able to do physical exercise appropriately. Thus the outcome and benefit of surgery may be compromised and the risk of postoperative morbidity, like deep vein thrombosis, lung embolism and pneumonia may be enhanced. Finally, it needs to be kept in mind that DMARDs usually have a long biological half-life. Based on the disease history and actual disease activity of the individual

patient, different time latencies after pausing DMARD therapy will be present until inflammatory exacerbation occurs. The physician is therefore often left in a dilemma. Finally, we would like to point out the difficulties in interpreting the literature concerning the perioperative management during immunosuppressive therapy. Different surgical procedures clearly confer different risks of perioperative infectious complications. In addition, the risk of infection depends on the duration, the location and the character of the surgery, for example, primary or revision. Furthermore, the definition of wound infection is not equally applied throughout the available publications. With respect to the consequences for the patient and overall economic considerations it seems to be reasonable to distinguish between superficial, deep and prosthetic infections. An estimated rate of overall perioperative infections in orthopedic surgery is estimated between 2% and 4% [8,9]. This number needs to be taken into account when looking at infection rates in patients under immunosuppressive therapy. However, the risk of deep wound infection may also depend on the type of surgery [8], body mass index, sex [10,11], race [12] and other comorbidities. However, comorbidities are not always appropriately documented [13].

This review discusses the present studies on perioperative management of immunosuppressive therapy. We also give our personal recommendations keeping the above mentioned points in mind.

Glucocorticoids

Since the introduction of glucocorticoids (GC) for the treatment of inflammatory diseases these drugs are an important cornerstone in the treatment strategy due to their quick-onset of anti-inflammatory and anti-proliferative effects and relatively easy handling. Furthermore, these drugs are rather cheap with respect to primary costs.

GC modulate different metabolic pathways by activating cytosolic and membrane-bound GC-receptors as well as nonspecific interaction of GC with cell membranes thus conferring genomic and non-genomic effects [14]. Therefore, GC mediate effects on every cell in the body. With respect to this review relating to wound healing and infection, GC inhibit, depending on the dosage and route of application, proliferation and function of immune cells, fibroblasts, and endothelial cells [15,16]. Protracted wound healing may predispose for an enhanced rate of infectious complications following surgery [17]. Up to date, it is not known at which daily or cumulative GC doses anti-proliferative effects with clinical relevance for delayed wound healing are to be expected. No systematic studies relating to this problem have been performed. However, the physiologic production of hydrocortisol in the adrenal glands amounts to about 9 – 11 mg/m2 per day [18] or roughly 1 mg/h. Therefore, dosages of about 7.5 mg of prednisolone per day might not be problematic with respect to protracted wound healing. The often cited recommendation of perioperative supraphysiologic GC replacement doses of Salem et al. [19] is not supported by evidence and was recently questioned [20] for its adverse effects on metabolism, immune function and anti-proliferative effects. However, it is common practice to give a stress dose of GC intraoperatively of about 3 times of the usual daily dose and tapering quickly over 2 to 3 days to the usual daily dose of GC. Furthermore, clinical judgment is necessary to adapt GC dosage as needed according to the specific situation.

Hydroxychloroquin and Chloroquin

The mechanism of action of this class of DMARD is not very well understood. In vitro studies have shown that lysosomal membranes are stabilized and cytokine production of IL-1 and TNF is reduced [21]. Additionally, an inhibition of complement activation is postulated.

There are contradictory data concerning the perioperative use of these drugs. Grennan and colleagues[22] found a higher rate of surgical infections in patients treated with anti-malaria drugs compared to methotrexate treated patients undergoing elective orthopedic surgery [22]. However, the number of patients treated in this analysis with anti-malaria drugs was quite

low, which limits the conclusion. Another study showed no difference in infectious complications after elective orthopedic surgery [23]. However, in this study the overall infection rate was quite high with 32%. Due to these contradictory data it is not possible to give sound recommendations on the perioperative management with anti-malaria drugs. Relating to the long half-life of about 40-50 days [24] and low toxicity profile of anti-malaria drugs, we continue to give these drugs to patients with surgery in an out-patient setting with anticipated quick recovery.

Sulfasalazine

The immunosuppressive mechanism of sulfasalazine is not well understood. Inhibitory effects on the function of neutrophils, monocytes, and lymphocytes have been described. Furthermore, anti-proliferative effects on fibroblasts and endothelial cells seem to play a role. These effects might be mediated by the sulfonamide component of the drug [25]. Von Broeder et al. [9] found a protective effect with respect to perioperative infectious complications probably due to the antimicrobial effect of the sulfapyridin, which is a sulfonamid derivative. It needs to be considered that sulfasalazine has a high plasma protein binding capacity of about 95% and can interfere with other drugs which bind to plasma proteins. Furthermore, there may be an additive hepatotoxic effect with certain drugs. If interaction with other drugs with high plasma protein binding or hepatotoxicity is of concern, we stop giving sulfasalzine two days (serum half-life about 8 hrs) before surgery and continue as soon as the clinical situation is stable. In general, we continue sulfasalazine treatment in patients with surgery in an out-patient setting with anticipated quick recovery.

Methotrexate

Methotrexate was first used as a DMARD in the early 1950s [26] to treat rheumatoid arthritis and psoriatic arthritis. It is used in a low-dose range from 5 to 25 mg per week and is considered as the DMARD with the best ratio of efficacy to toxicity [27]. Therefore, MTX is widely used in monotherapy as well as combination therapy and is considered reference substance to evaluate effectivity and toxicity of other DMARDs or biologics.
MTX modulates numerous immune mechanisms. MTX is a derivative of folic acid and is taken up by cells via the membrane bound folic acid transporter. Intracellularily, MTX is polyglutaminated (MTX-glu), explaining the long biologic half-life of intracellular MTX-glu. It inhibits competitively and reversibly the enzyme dihydrofolate reductase (DHFR) and

modulates the purine metabolism resulting in a cell cycle arrest in the S-phase in dividing cells. Within the low-dose range, this anti-proliferative effect does not play the main part with respect to immunomodulation. Numerous studies demonstrated proapoptotic effects, inhibition of expression of adhesion molecules, modulation of pro- and anti-inflammatory cytokine milieu, reduction of antibody production, as well as inhibition of cyclooxygenase activity. Furthermore, MTX inhibits numerous other enzymes like the 5-aminoimidazol-4carboxamid-ribonucleotid(AICAR)-transformylase. This enzyme catalyzes degradation of adenosine. By inhibiting AICAR, MTX increases the intra- and extracellular adenosine concentration. This leads to an adenosine-receptor cAMP-mediated inhibition of immune mechanisms.

Summarizing, MTX seems to modulate numerous immune mechanisms without completely abrogating them. This might explain, why most available studies did not show enhanced infectious complications despite continuous MTX-treatment in the perioperative setting (**table 1**). Only the prospective study of Carpenter et al. [28], unfortunately with small numbers, showed no infectious complications when MTX was paused 7 days perioperatively but 25% infectious complications when MTX was continuously given. However, except of the group treated continuously with MTX in the study of Grennan et al [22] overall infectious complications are above 4% in all studies whether MTX was paused or not. This observation goes along with a study of van der Veen et al, showing, that respiratory and skin infection rates among MTX treated patients are higher compared to infection rates among MTX-naive RA patients with both groups having the same prednisone daily doses [29].

However, based on the available data and on practicability grounds, we continue MTX in patients with surgery in an out-patient setting with anticipated quick recovery. If a more complex surgical intervention is required, we stop MTX treatment the week before and continue MTX the week after surgery, if no clinical infection or disturbance of wound healing occurs. However, if prolonged surgery or artificial respiration is anticipated or pulmonary comorbidity is present, we pause MTX until full recovery to reduce the risk of pneumonia. No safe timely pause intervals for MTX can be concluded from the literature.

Leflunomide

Leflunomide reduces de-novo-pyrimidine synthesis by inhibiting the enzyme dihydroorotat-dehydrogenase in the mitochondria [30]. The anti-proliferative effect is most evident in lymphocytes, and Kraan et al. [31] demonstrated that interferon-γ concentrations in the serum

are significantly reduced during long-term therapy. Furthermore, in vitro studies revealed inhibitory effects on certain tyrosin kinase enzymes [32], nuclear transcription factor kappaB and others [33].

Leflunomide mainly is used in monotherapy but combinations with other DMARDS or biologics are used in practice [34-36] although combinations are not recommended by the manufacturer with regard of additive hepato- and haematotoxicity. As already stated in the introduction, combination therapy is more prone of infectious complications compared to monotherapy. This may also be true with respect to infectious complications post surgery [37]. A prospective study analyzed wound healing complications after orthopaedic surgery comparing patients treated with either MTX or leflunomide [38]. The authors found wound healing complications in 13.6% of patients (59 patients) in the MTX group compared to 30,6% of patients (32 patients) in the leflunomide group. Considering 4% overall perioperative infectious complications in RA patients as stated in the paper of Broeder and collegues [9], there was an overall higher rate of wound healing complications in both groups. Another study showed no enhanced post operative infectious complications. The study compared continuous leflunomide treatment (82 patients) with a 4 week pause of leflunomide prior to surgery (79 patients). Patients of the first group developed in 6.1% infectious complications, whereas this rate was 6.3% in the second group. No deep tissue infections were recorded in both groups. In the light of the long half-life of leflunomide, these results seem reasonable although the number of patients was relatively small. However, a wash-out phase of leflunomide, e.g. with cholestyramine in patients at higher risk of infectious complications has not been addressed in the literature yet.

The available data does not allow drawing definite conclusions whether to stop, continue or wash out leflunomide prior to surgery. It is up to the judgment of the physician on how to deal with this drug in a perioperative setting according to the disease history of the individual patient, the nature of the planned surgery, comorbidity, and history of wound infections in the past. We suggest, if in doubt, to wash out the drug due to the long half-life [39].

TNF-Inhibitors

As with all other drugs, it is not possible to give a definite recommendation for a structured pause of anti-TNF drugs in the perioperative setting. However, in the study of Broeder et al [9] no statistical difference of infectious complications could be found between the groups of continued and paused anti-TNF therapy. Another study showed similar results [40] as no enhanced infectious complications were detected between paused or continued anti-TNF

therapy. However, there also is a contradictory study published byGiles et al [41]. In this study, 70% of patients developing infectious complications were treated with anti-TNF drugs. In contrast, 65% of patients without infectious complications were not treated with any anti-TNF drugs in the past. Similarly, data of the British Register of the Society for Rheumatology detected an increased risk of soft tissue and skin infections in anti-TNF treated patients with and adjusted incidence ratio of 4,28 (95% confidence interval 1.06-17.17) [42]. In this register 7664 RA patients treated with anti-TNF drugs and 1354 patients treated with other DMARDs are documented. Another retrospective study evaluated the complication rate in patients with continued and paused anti-TNF therapy. The results revealed higher complication rates in orthopaedic and abdominal surgery even when the anti-TNF drug was paused for 2 -5 half-lifes prior to the procedure [7].

However, from a practical stand point of view, we use a compromise by pausing anti-TNF medication 4-5 half-lifes prior to surgery and start treatment after recovery from surgery.

Summary

The difficult question whether to continue or to stop immunosuppressive medication prior to an elective surgery is common daily practice. Due to the nature of these drugs, the immune system of the patient is more or less intensely suppressed to control the chronic inflammatory process. The down side may be a reduced response to infectious organisms especially in the situation of surgery which is by itself associated with an immunosuppressive situation. So if one had the choice, one would stop these drugs prior to surgery to lower the risk of infectious complications as much as possible. Unfortunately, pausing DMARDs and biologics may provoke inflammatory exacerbation of the underlying condition, which usually is followed by increasing the immunosuppressive medication. How fast and if at all disease exacerbation will occur after pausing DMARD or biologic therapy, is up to the individual patient. However, exacerbation is usually answered by increasing the GC dosing for the rapid onset of anti-inflammatory activity which, as mentioned above, is not favorable for the healing process of the surgical wound. Therefore, when guiding immunosuppressive therapy in chronic inflammatory diseases, we need to take the golden way to do as little immunosuppression as possible and as much as necessary. For each drug, we find evidence in the literature supporting either one of our decision. Therefore, it is at the responsibility and expertise of the physician to come up with a decision according to the special situation of the patient. The dialog between the surgeon, rheumatologist, health practitioner and the patient is most

important. The individual patient´s situation needs to be evaluated according to the actual health and disease status, the urgency, necessity, and nature of the planned surgery, infectious complications in the past, the degree of immunosuppression and comorbidity. According to our experience, we recommend that if in doubt to stop the drug for 4-5 half-lives or, in the case of Leflunomide, perform a wash out with cholestyramine because deep wound infections or prostheses infections may have deep impact on the patients well being. However, because of the long biologic half-life of many DMARDs, this recommendation is not based on good scientific data. Nevertheless, this procedure is practical and according to our experience with respect to infections and inflammatory exacerbation we feel rather comfortable. In all patients, whether immunosuppressive medication is continued or not, high suspicion for infectious complications must always be present to quickly institute diagnostic and therapeutic procedures.

Legend

Table 1

The table summarizes the literature with respect to infectious and wound healing complications with no immunosuppression, paused, and continued methotrexate therapy in the perioperative setting.

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Table 1

Operative procedure	Number of procedures	Infectious and wound healing complications			Study-design	Author (year)
		No immunosuppression (number of procedures)	Continued (number of procedures)	Paused time before surgery (number of procedures)		
Joint replacement	34			0% >4 weeks (34)	retrospektive	Bridges 1991 [43]
Joint	19			21%		

replacement				< 4 weeks (19)		
Joint replacement of large joints	202		8,7% (92)	5,5% (110)	retrospektive	Perhala 1991 [44]
Orthopaedic surgery	89		10% (39)	12% 7 days (50)	prospektive	Sany 1993 [45]
Joint replacement	42		25% (16)	0% 7 Tage (26)	prospektive	Carpenter 1996 [28]
Joint replacement	388	10,5% (228)	2% (88)	15% (72)	prospektive	Grennan 2001 [22]
Hand surgery	99	9,5% (21)	5,1% (78)		retrospektive	Jain 2002 [46]
Orthopaedic surgery	201	11,7% (103)	5,2 (77)	14,3 > 7 Tage (21)	retrospektive	Murata 2006 [47]