Pain and inflammation. Part 2. The analgesic potential of anti-inflammatory drugs

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An inflammatory response and the development of pain are interdependent processes. Inflammation accompanied by the overproduction of proinflammatory cytokines and mediators not only causes pain, but is also the main cause of its chronicity. Therefore, the use of anti-inflammatory drugs should be considered to be the mainstay of analgesic therapy. Part 2 of the review discusses the analgesic potential of various pharmacological groups that have an anti-inflammatory effect: nonsteroidal anti-inflammatory drugs, glucocorticoids, biological agents, methotrexate, slow-acting antiinflammatory drugs (chondroprotectors), as well as a number of promising and experimental agents, such as nerve growth factor inhibitors. It provides data from major clinical trials that have evaluated the analgesic effect of these drugs in various diseases and pathological conditions.

Key words: pain; inflammation; paracetamol; nonsteroidal anti-inflammatory drugs; glucocorticoids; methotrexate; biological agents; nerve growth factor inhibitors.
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In the first part of the present review the key role of inflammation in the development of pain is represented. Proinflammatory cyrokines and mediators, such as prostaglandin (PG) E2, not only induce and enhance the pain sensation associated with the damage of living tissue due to direct activation and the sensitization of peripheral nociceptors. The uncontrolled inflammatory reaction triggers the process of the chronic pain generation, which is associated with the phenomena of the central sensitization and neuroplasticity. It becomes obvious that the main direction of complex analgesic therapy should be the targeted use of pharmacological agents possessing the anti-inflammatory potential [1–3].

Currently in the arsenal of a doctor there is a wide range of drugs that can block the development of an inflammatory reaction. They include non-steroid anti-inflammatory drugs (NSAIDs), glucocorticoids (GC), anti-cytokinic drugs as well as Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOA, previously referred to as «chondroprotectors»). Furthermore, there are various drugs for the «point» exposure on individual inflammatory mediators being developed and in the stage of clinical approbation.

Paracetamol and NSAIDs

The analgesic effect of paracetamol (acetaminophen), the most popular analgesic in the world, is associated with its ability to block cyclooxygenase (COX) 2 in the CNS tissue [106]. Some authors also mention its effect on the particular species of an inducible form of COX, spe-

cific for the brain, COX-3, as well as its ability to act as a ligand of the endocannabinoid system [4–6]. The peripheral anti-inflammatory effect of paracetamol is poorly expressed. And although paracetamol is commonly recommended as a first line therapy for relief of pain with osteoarthritis (OA) and low back pain (LBP), its analgesic potential is relatively small, and the main advantages are the good tolerability and the possibility of the over-the-counter use. The data of the recently issued meta-analysis of 13 randomized controlled clinical trials (RCTs), comparing effects of paracetamol and placebo for LBP and OA, demonstrates the low efficacy of this drug. Thus, the reduction of the pain severity on the 100-mm visual analogue scale (VAS) when using paracetamol for LBP differed from placebo only by 0.5 mm (95% confidence interval, CI 1.9–2.9), and by 3.7 mm (95% CI 1.9–5.5) for OA. It's necessary to note, that the risk of the increase in alanine aminotransferase, ALT (that means its possible negative impact on liver) when using paracetamol was nearly 4-fold higher, than in those received placebo – 3.8 (95% CI 1.9–7.4) [7].

NSAIDs, the large class of selective and non-selective inhibitors of COX-2, are most widely used in clinical practice for relief of pain related to injuries and peripheral inflammation. Their efficacy is beyond doubt: the use of NSAIDs for acute/subacute LBP and OA at moderate to high therapeutic doses allows attaining the significant improvement (reduction of pain severity by 50% of the baseline) in 40-50% patients. The NSAIDs analgesic potential for LBP and OA is higher, than for paracetamol and not inferior to the analgesic effect of «weak» opioid drugs, such as tramadol [8–10].

The use of NSAIDs for rheumatoid arthritis (RA) is less effective – according to data of RCT dynamics of the severity of pain on the average is 25%. The effect of NSAIDs on systemic inflammation is much less pronounced. This is demonstrated, in particular, by a large-scale RCT, during which 1171 patients with RA who received 90 mg/day etoricoxib, 1000 mg/day naproxen or placebo for 12 weeks. As compared with placebo, the active therapy allowed to significantly reduce pain and improve the patients' condition. But the number of inflamed joints, which was on the average 19 (of 66 evaluated) in each of studied groups when treating with etoricoxib and naproxen, decreased only by 1.43 and 1.39; the mean level of C-reactive protein (CRP) *slightly increased* as compared with the placebo group, wherein in those receiving etoricoxib this increase (by 1.11 mg/ml) appeared to be statistically significant [11].

The absence of any positive effect of NSAIDs on the CRP level with RA is confirmed by the meta-analysis of 19 RCTs, in which the efficacy of 10 different representatives of this group was studied. Only one NSAID, naproxen, demonstrated the small, but significant and constant decrease in the CRP level [12].

However, with other inflammatory rheumatic diseases, for example, for ankylosing spondylitis (AS), the anti-inflammatory and analgesic effect of NSAIDs is significantly higher, which allows them to be considered as the main pathogenetic agent. In contrast to RA, the use of NSAIDs for AS significantly decreases the concentration of CRP [13, 14].

The clear evidence of the NSAIDs high anti-inflammatory potential is their efficacy in relief of gout arthritis attacks [15]. With this pathology, characterized by acutest metabolic inflammation associated with the IL-1β overproduction and massive activation of M1 macrophages, the efficacy of NSAIDs at standard doses is not inferior, than the efficacy of GC at high doses (see below) [16].

The analgesic effect of NSAIDs is mainly related to its ability to reduce the severity of peripheral inflammation and the sensitization of nociceptors. To the most extent this is determined by the inhibition of the synthesis of PGE2, one of the main pain and inflammatory mediators. Furthermore, for NSAIDs the following effects were described: decreased expression of COX-2 and prostaglandin receptor EP 1-4 RNA, decreased synthesis of cytokines (including IL-6), inhibition of inducible NO-synthetase, constraining of proinflammatory signaling pathway (in particular, associated with NF-κB activation), catabolic effect due to blockade of the mitochondrial enzymatic system, apoptotic stimulation, and also – due to the effect on the synthesis and the exertion of effects of growth factors, the inhibition of neoangiogenesis and the development of heterotopic ossification [1, 17].

It should be noted, that NSAID can exert their effect also on central mechanisms of pain formation. As noted above, one of the most important mechanisms for the formation of the phenomenon of central sensitization is determined by the production and the accumulation of proinflammatory mediators in the CNS tissue; among them the leading role is played by PGE2. NSAIDs can penetrate the blood-brain barrier (by their free, albumin-unbound fraction) and create in the CNS tissue the sufficient concentration for effective blockade of the synthesis of COX-2 and the inhibition of the synthesis of PGE2 [2, 3,18]. Experimental works clearly confirm the analgesic effect of NSAIDs associated with their effect on the synthesis of proinflammatory mediators in the CNS [2, 3, 19, 20].

There are only a few clinical trials assessing the efficacy of the «central» administration (directly to spinal cord structures) of NSAIDs for relief of acute and chronic pain. These works showed controversial results. Thus, the use of the intrathecal administration of ketorolac in three controlled studies (two with chronic pain during the intrathecal morphine therapy, one – with acute pain after a surgery, 57 patients in total) showed no significant difference in the effect of this drug, as compared with placebo [21].

The main drawback of NSAIDs is the significant risk of the development of dangerous gastrointestinal (GI), cardiovascular (CV) and renal adverse events (AE) [9, 22, 23]. This problem significantly limits (and in some cases makes it impossible) the use of this class of analgesics in patients with serious comorbid pathology, primarily in elderly people with cardiovascular pathology and significant renal disorders.

Glucocorticoids

GCs are one of the most widely used drugs in the world. About 0.5% of the global population constantly receives them, and in some groups they are used essentially more widely (among women aged above 55 years old - about 1.5%). Irrespectively of active distribution of biological therapy, GCs hold down their position as the most important agent for the treatment of rheumatic diseases. Thus, from 15 to 90% patients with RA intake them, the majority of patients with systemic lupus erythematosus (SLE) and polymyositis, almost all of the patients with polymyalgia rheumatica and vasculitis [24].

The anti-inflammatory effect of GCs is carried out by means of two main pathways. In the long, «genomic» pathway lipotropic molecules of GC penetrate the cellular membrane and interact with the specific cytosolic receptor (GCR). The formed complex moves freely into the nucleus, where it exerts two, generally opposite, effects towards the DNA action. On

the one hand, it triggers mRNA transcription, providing the synthesis of a number of proteins, modifying the cellular metabolism; for another hand, it blocks the interaction of a number of the most important signaling molecules (NF-κB, AR-1, IFR-1), activating the expression of proinflammatory cytokines, with DNA. The genomic pathway is carried out under exposure of low doses of GC (<7.5 mg/day in prednisolone equivalent), and the effect after contacting of GC with the target cell develops approximately after 30 min [24–26].

Another, «non-genomic» pathway for the anti-inflammatory effect of GC exhibits with their use at high doses (>30 mg/day in prednisolone equivalent). In this case the impact of GC is mediated by membrane receptor, as well as with the non-specific interaction with membranes of cellular organelles, in particular, mitochondria. This pathway of the exposure provides the significantly more rapid effect, which is noted already within first minutes, for example, with the intravenous (i.v.) administration of mega-doses of GC (pulse therapy) [24–26].

Usually GCs are considered only as an anti-inflammatory agent. However, these drugs have the serious analgesic potential. In particular, with RA the analgesic effect of systemic GCs is higher than of NSAID. It is demonstrated by the data of the meta-analysis of 10 RCTs (n=320), in which the efficacy of oral intake of GC at a dose of < 15 mg (in prednisolone equivalent), NSAID and placebo during the first month after prescribing was compared. As compared with placebo and NSAID, GC more efficiently reduced the number of painful joints: to the end of the follow-up period their number differed on the average by 12 and 9 ($p<0.001$), and also more efficiently increased the strength of grip – by 22 and 12 mm Hg, respectively (the significant difference only in relation to placebo) [27].

The good symptomatic effect of GCs justifies their use with RA onset for attaining the rapid effect and comfortable waiting of the onset of action of Disease-Modifying AntiReumatic Drugs (DMARDs), such as methotrexate (so called «bridging therapy»). The use of GCs may be also indicated with high, poorly controllable activity and the development of systemic manifestations; in the last case the short-term use of mega-doses of these drugs is appropriate (pulse therapy). However, as the effect of GCs on RA progression is at least doubtful, and the risk of the development of AE is sufficiently high, the current concept of the use of these drugs intends gradual tapering of the dose and, as possible, their total withdrawal after attaining of the low activity and the remission on the background of properly selected therapy with DMARDs [25].

The systemic and local administration of GCs is sufficiently widely used for relief of acute gout arthritis. True, according to the data of two RCTs (n=210), oral administration of high doses of GC (>30 mg in prednisolone equivalent) had no advantage in reducing pain and inflammation, as compared with NSAID [15, 16].

There are a few works, in which the efficacy of systemic administration of GC for LBP and OA. Friedman B. et al. represented the data of RCT, during which 82 young (under 50 years of age) patients with sciatica were given once intramuscularly (i.m.) 160 mg methylprednisolone or placebo. The significant improvement was more frequently noted in the active treatment group: the probability of a good response was 1.3; however no statistically significant difference was found ($p=0.1$). It's necessary to note, that i.m. injection of GC reduced the need for analgesics (up to 22% and 43% cases in the active treatment and in the placebo group), and also decreased functional disorders (up to 19% and 49% respectively). However, AEs were also noted more frequently in the active therapy group – 32% and 24%, respectively [28]. Recently the results of the study by Abou-Raya A. et al. were published, where the therapeutic effect of oral intake of prednisolone 7.5 mg/day and placebo was compared in 125 patients with knee OA. After 6 weeks of therapy the significant difference in dynamics of pain, condition and performance status between groups was noted. Thus, the difference in reducing of the severity of pain sensations was 10.9 (CI% 4.8–18.0) mm on the 100-mm VAS, $p < 0.001$ [29].

Nevertheless, the appropriateness of the wide use of systemic GCs with LBP and OA cause doubt, primarily because of the risk of the development of serious complications. Much more widely GCs are used as local injections allowing the delivery of an active substance directly to the inflamed area and reducing the probability of systemic AEs.

There is no doubt about the efficacy of local injections of GCs [30–32]: their use is recommended by Russian and foreign experts for the treatment of major joint OA [33, 34]. A good evidence of the high therapeutic potential of GCs injections was a meta-analysis of 63 RCTs (n=14,060), in which the effectiveness of different pharmacological methods for OA with the follow-up to 4 weeks. Thus, intra-articular administration of GC has maximally reduced the intensity of pain contrary to placebo: on the average 14.5 mm on the 100-mm VAS, that was higher than the effect of NSAIDs (10.2 mm), opioids (10.5 mm) and paracetamol (4.7 mm) [35].

True, local administration of GC provides only a short-term improvement [36, 37]; furthermore, multiple injections can lead to atrophy of soft tissues and development of such pathology as ligament rupture and acceleration of OA progression. Therefore injections of GC should not be performed more than 2–3 times a year to the same anatomical object [34]. Furthermore, the systemic effect of GC can result in the increase of BP and glucose level (that is important for those suffering with diabetes mellitus), as well as other AEs [38–41].

Local injections of GCs and topical anesthetics are widely used for the treatment of backache. This technique has an important diagnostic and therapeutic significance with so called «facet syndrome» (LBP, caused by facet joint OA), as well as for pain relief with sciatica and spinal stenosis. However, according to the data of the series of RCTs injections into the region of the facet joints, nerve roots and into the epidural cavity provide only short-term relief of sufferings and relatively little effect on the performance state of patients and late fate [42–44]. Furthermore, local injections can cause although sufficiently rare but extremely dangerous neurological and septical complications [45, 46]. Therefore this method for LBP treatment should be used for clear indications, by high experienced specialists aseptically, with the obligatory use of instrumental visualization.

Methotrexate

Methotrexate (MT) is the main representative of the DMARDs class, widely used with various diseases of autoimmune or immunoinflammatory nature. The special value of MT is for the treatment of RA, wherein it is considered as a first line medication in the implementation of the modern concept of management of patients with this severe illness – «treat to target» therapy up to attaining remission or persistently low activi-

ty [47]. The active use of MT for the RA onset allows attaining remission in approximately 30–50% patients. Even in the case when MT monotherapy does not result in a complete therapeutic success, and biological therapy administration is needed, its anti-inflammatory and immunomodulating effect creates a basis for more the more effective use of the latter. The combined use of MT and biological therapy not only significantly increases the effectiveness of treatment, but also promotes maintaining the therapeutic potential of the latter. Indeed, biological therapy have a proteinaceous nature (see below), therefore the most important factor, reducing their efficacy, is production of blocking antibodies by patient's immune system. MT is able to prevent or delay this process [48].

The pharmacological action of MT is associated with its antimetabolic effect: its ability to play the role of folic acid antagonist and to block the dihydrofolate reductase enzyme, thus interrupting the formation of folates, the synthesis of DNA and RNA. However, this rough mechanism is realized only with the use of high («oncological») doses of MT. With rheumatic diseases, when using MT at relatively high doses no more than 30 mg/week, it's effect on immune inflammation appears to be more «fine» and multi-attribute. This is an inhibition of the synthesis of folat-dependent proteins playing an important role in the development of inflammatory reaction, intracellular signaling pathways blocking (including through the effect on protein kinases JAK1-3 and Tyk2), binding of protein DAMS (in particular, HMGB1), decreased synthesis of proinflammatory cytokines IL-1β, IL-6, tumor necrosis factor (TNF)-α and others. MT is able to indirectly inhibit the differentiation of T-helper and activation of antibody producing B-cells and enhance the inhibitory function of T_{per} cells [48, 49].

MT is primarily considered as a proinflammatory agent, the use of which is directed to delay of disease progression. As in the case with GC, physicians rarely think over the presence of own and sufficiently potent analgesic potential of MT. The ability of MT monotherapy to sufficiently reduce activity, severity of pain and improve joint function is confirmed by the results of the recently issued meta-analysis of 7 RCTs (n=732), in which MT is compared with placebo during the follow-up duration up to 52 weeks [50].

The good symptomatic effect of MT is of great value for 'real-life' clinical practice – it's obvious, that the active use of this drug allows sufficiently reducing the need in other analgesic, primarily NSAIDs. Also the latter provide the rapid reduction of main RA symptoms; they represent rather dangerous analgesics, especially in individuals with cardiovascular risk factors. On the contrary, MT is able to reduce the risk of progression of CV diseases and the development of cardiovascular events [48]. Of course, the therapeutic action of MT develops gradually, and this is an obvious drawback for a drug being used for analgesia. On the other hand, the rate of MT effect occurring depends on its formulation. It is well known that subcutaneous (s.c.) administration of MT provides more stable pharmacokinetics, which increases the treatment effectiveness and reduces the risk of the development of. The formulation of MT for s.c. administration provides the more rapid and potent analgesic effect [48].

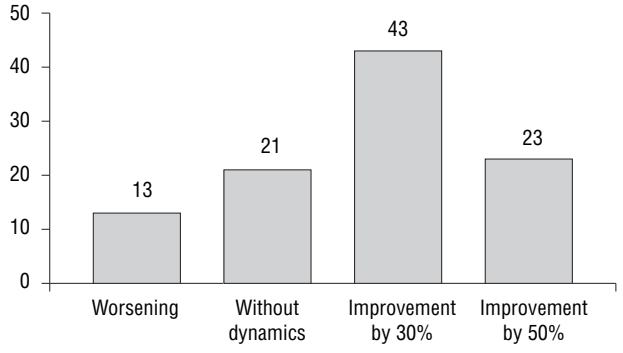

Figure 1. Efficacy of methotrexate 20 mg/week for knee OA (n=30, 24 weeks), adapted from [53]

This fact is clearly confirmed by the work by Li D. et al. representing the meta-analysis of 7 RCTs (n=1335), in which the effect of oral intake and s.c. administration of MT for RA was compared. As compared with oral intake, s.c. injections provided the significantly higher reduction of the disease activity (improvement by 20% and 70%), odds ratio (OR) = 1.68; 95% CI 1.09-2.61 and 1.52; 95% CI 1.02-2.26. The similar situation was observed for pain relief: the mean difference (MD) was = -0.65 (95% CI -0.93 – -0.37) [51].

MT represents a great interest also for the treatment of OA, considering the role of chronic inflammation in the development of pain and progression of structural modifications with this disease [52]. There is a small but extremely interesting experience of the use of MT for OA. Thus, Wenham C. et al. assessed the results of the use of 20 mg/week MT in 30 patients with knee OA during the open 24-week study. The inclusion criteria was the presence of severe pain (on the average 68 mm VAS), as well as ineffectiveness or intolerance of NSAIDs and opioids. The therapy with MT provided the significant improvement of the condition in majority of patients: the reduction of pain at least by 30% was observed in 66% subjects of the study (Fig. 1) [53].

Probably, the further works will allow determining the place of MT in OA therapy more accurately. In the present time a large-scale, multicentre, 12-month RCT PROMOTE is being conducted by British scientists, wherein the effect of MT (up to 25 mg/week) on dynamics of pain in knee OA will be investigated [54].

Biological therapy

Last years, there have been revolutionary changes in the treatment of immunoinflammatory diseases and cancers. They are related to the development of the «target therapy» concept, the targeted pharmacological intervention in a disease mechanism, when targets for drugs are particular cellular elements or humoral factors, playing the key pathogenetic role. The main agents for this are biological therapy, representing monoclonal antibodies (MAbs) or soluble receptors, blocking certain cytokines or receptors on the surface of immune system cells [55, 56].

Biological therapy (inhibitors of TNF-α, IL-1, IL-6 and others) possess the potent anti-inflammatory potential and the ability to stop disease development (this effect is definitely expressed with RA). Their use significantly reduces the severity of painful sensations with RA and AS. This was demonstrated, in particular, by the meta-analysis of 17 RCTs, in which the effect of different biological therapy (as compared with placebo and MT) on subjective, self-assessed parameters of the RA activity was studied. Thus, it was shown, that monotherapy with TNF-α inhibitors (infliximab, adalimumab, etanercept and others) and IL-6 inhibitor (tocilizumab) after 24 weeks provided the reduction of pain severity by 20-30 mm on 100-mm VAS. The combined use of biological therapy and MT provides the even higher analgesic effect, Fig. 2 [57].

Of course, biological therapy have certain drawbacks. These are the very high cost and the risk of the development of a wide range of sequellae, among which activation of opportunistic infections, in particular, tuberculosis, has the greatest medical and social significance. Nevertheless, their use is consistently expanding, and today the majority of experts consider biological therapy as the most important tool in treating diseases of autoimmune and immunoinflammatory genesis.

The success of biological therapy with RA and AS has led to attempts of the use of these drugs for OA and LBP as well. Thus, a serious evidence of the key role of IL-1β in the development and progression of OA caused the idea to test anakinra, the recombinant inhibitor of IL-1 receptor (IL-1Ra), for this pathology. However, the clinical trial by Chevalier X. et al. did not confirm any efficacy of this biological therapy. In the duration of the work 170 patients with prominent knee OA received one intraarticular (i.a.) injection of 50 mg or 150 mg anakinra or placebo. Treatment outcomes were assessed after 4 weeks. Unfortunately, no significant improvement of the condition (according to dynamics of index WOMAC) in those received the active therapy as compared with the placebo group was observed [58].

An experience of biological therapy inhibitors of TNF-α for LBP and sciatica was not sufficiently successful as well. This fact was shown by the work by Pimentel D. et al., representing the meta-analysis of one observational study (n=143) and 11 RCTs (n=539), in which the effect of epidural administration of TNF-α inhibitors and placebo was compared. The test drugs were etanercept, adalimumab, infliximab and investigational REN-1654. As appeared, the statistically significant difference from placebo for dynamics of painful sensations was observed only in 5 RCTs, wherein the level of effect was assessed as moderate or small [59].

The new target for pharmacotherapy of pain with chronic disease appears to be nerve growth factor (NGF). At present several biological medications - tanezumab, furlanumab and fasinumab (REGN475), representing monoclonal antibodies, capable to block this factor and thereby significantly reduce the pathological hypersensitivity for pain, has been developed [60]. The series of large-scale RCTs has confirmed the high efficacy of the novel class of analgesic drugs for OA. The well-studied of NGF inhibitors appeared to be tanezumab: this drug is administered i.v. at 5 or 10 mg once in 2 months. The series of large-scale, well-organized RCTs, in which thousands of patients with knee and hip OA have been enrolled, clearly showed its advantage, especially in combination with NSAID, as compared with NSAID monotherapy (naproxen, celecoxib and diclofenac) or opioids (oxycodon). However, in the studies performed, unfortunately, a number of drawbacks of tanezumab were found, which eventually discontinued obtaining of marketing authorization and starting to use in real clinical practice. It appeared that the novel drug causes serious AEs – appearing of sensory symptoms (paresthesia and hypesthesia), in a number of cases appearing or worsening of polyneuropathy, as well as accelerating of OA progression, which in individual cases required performing of joint replacement [61–63].

There were performed 4 RCTs, in which the efficacy of three different NGF inhibitors – tanezumab, furlanumab and fasinumab (2109 patients in total) for LBP was investigated. The results of this work appeared to be rather modest – only tanezumab demonstrated the significant, also relatively small, analgesic activity. The normalized difference of mean values for the significant clinical response in tanezumab and placebo groups was -0.44 (95% CI -0.81 – -0.07), corresponding to only modest difference. At the same time, the number of AEs with the use of NGF inhibitors (primarily, neurological), appeared to be significantly higher than with placebo: OR was 1.93 [64].

SYSADOA

Drugs of this series – glucosamine sulphate, chondroitin sulphate, diacerein and unsaponifying compounds of avocado and soybeans are generally used in complex therapy of major joint OA. According to contemporary ideas, their pharmacological effect is associated with the inhibition of «cytokine cascade» activation by them, which accompanies the development of chronic inflammation and the destruction of cartilaginous tissue [65, 66]. Therefore SYSADOA can be classified as anti-inflammatory drugs.

The analgesic effect of most SYSADOA develops gradually and becomes significant not earlier than after 1–2 months since starting intake. The reduction of pain severity attainable with the use of drugs of this series is relatively small and generally is not higher than 20–25% of the baseline. However, administration of SYSADOA in combination with rapid analgesics – paracetamol or NSAID allows to significantly improve the results of therapy, decrease the dose of the latter and gradually withdraw them at all [67–70]. At the present time there is a steady tendency to expand the scope of SYSADOA application – they are more and more frequently used just as peculiar analgesics, for example, for backache [71, 72]. The main advantage of these drugs is good tolerability and the absence of serious AE, thus allowing their administration even with severe comorbidities in patients. This is especially important for analgesic therapy in people with OA and who have contraindications for NSAID administration – for example, in the presence of clinically severe ischemic heart disease, experienced cardiovascular events or chronic renal disease with a low glomerular filtration rate.

Other targets of anti-inflammatory therapy

At the present time due to the success of pharmacology a wide range of molecules, capable for blocking the negative impact of main mediators of pain and inflammation was created. However, only a small part of these developments became effective analgesic drugs available for use in clinical practice. Many promising substances did not go beyond the limits of pharmacological laboratories, or their way has stopped on the level of phase 2–3 clinical trials. Such a fate befell, for example, licofelone, a double inhibitor of COX-2 and 5-LOX, capable for blocking the synthesis of leukotrienes (LTE). Some

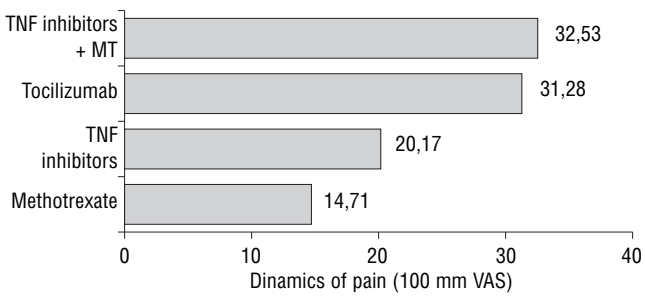

Figure 2. Analgesic effect of biological therapy and MT for RA (meta-analysis of 17 RCTs, 24 weeks), adapted from [57]

experts consider that licofelone possesses the marked advantage in tolerability, as compared with conventional NSAID, first of all, towards GI tract [73]. Furthermore, the blockage of 5-LOX is capable to affect the development of «cytokine cascade», underlying progression of rheumatic diseases [74]. In the large-scale 2-year RCT, wherein licofelone was compared with naproxen in 355 OA patients, the novel drug demonstrated not only a good analgesic action, but also a distinct slowing down of the destruction of articular cartilage [75]. Unfortunately, this drug was not approved for clinical use; therefore an assessment of its therapeutic potential remains a matter of the future.

The promising inhibitor of platelet activation factor, israpafant [76], and the series of anti-histamine drugs of a new generation, capable for blocking H4-receptors [77, 78], while remains at the level of laboratory development. Clinical trials of synthetic drugs, capable for blocking calcitonin gene related peptide (CGRP) receptor - telcagepant and olcegepant, as well as monoclonal antibodies against the CGRP molecule and its membrane receptors, are ongoing. With these medicines, there are great hopes for the treatment of migraine [79–81].

It is interesting to note, that a number of drugs approved and entered clinical practice, which are antagonists of such important mediators of pain as leukotriene, bradykinin, serotonin and substance P, possess no direct analgesic effect and are used for other indications. Thus, blockers of receptors of cysteine-containing LTEs ($LTEC_4$, $LTED_4$, $LTEE_4$) – cysLT1, such as zileuton, zafirlukast and montelukast, are used for bronchial asthma [82, 83]. Icatibant (bradykinin B2-receptor blocker) is approved as an agent for the treatment of hereditary angioedema [84]. Inhibitors of serotonin (5HT) receptors are potent anti-emetics, which are actively used in gastroenterology as anti-emetic agents during chemotherapy in oncology [85]. NK1-blocker aprepitant, the antagonist of substance P, has occupied the same position [86]. It is curiously, that last years, works pointing out the efficacy of this drug or treating experimental arthritis in primates, has appeared [87].

Great hopes are associated with the creation of selective inhibitors of m-PGE2 synthetase, the enzyme responsible for the final step in the synthesis of PGE2, the most important mediator of pain and inflammation, as well as inhibitors of receptors of that prostaglandin – ER2 and ER4. Such drugs would possess properties of «super-NSAID», exerting a potent analgesic and anti-inflammatory effect and not causing GI and CV AEs, characteristic for conventional NSAIDs. Now pharmacologists conduct an active work in this field [88–91].

Another important direction in developing promising anti-inflammatory drugs may become the creation of artificial analogues of resolvins, the most potent endogenous regulators of the inflammatory reaction. These drugs can realize a completely different, other than modern, concept of anti-inflammatory therapy: not inhibiting inflammation but stimulating its natural resolution [92, 93]. The first drug in this group – RX 10045 (the stable analogue or resolvin E1), undergoes clinical approbation for the «dry eye» syndrome [94].

Conclusion

The main trend in analgesic therapy is the use of drugs possessing an anti-inflammatory effect. Conventionally NSAIDs and local injections (less frequently systemic administration) of GC are used as a symptomatic analgesic agent. But there is a serious analgesic potential for MT and anti-cytokine biological therapy, TNF-α, IL-1β, IL-6 inhibitors. Rational use of these drugs can reduce the need for NSAID and GC, thereby eliminating the risk of the development of serious AE associated with the latter. And, although MT and biological therapy are usually considered as agents for pathogenetic therapy of autoimmune and immunoinflammatory diseases, there is an experience of their use for pain relief with OA and LBP.

The effect of SYSADOA also should be contemplated in the context of a «mild» anti-inflammatory effect. Although an «application point» of these drugs is the treatment of OA, nevertheless, they are more and more widely used in complex treating of pain with chronic LBP.

By no means all drugs, capable for blocking biological effects of pain and inflammatory have found practical use as analgesic agents. This concerns inhibitors of LTE, bradykinin, substance P and others. On the other hand, we can expect that in the near future the arsenal of analgesic therapy will become essentially wider due to absolutely novel classes of medications, such as NGF inhibitors, selective inhibitors of PGE2 synthetase, artificial analogues of resolvins and others.

Transparency

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